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TREATMENT OF SEVERE HYPERTENSION WITH GUANETHIDINE.

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THE search for the ideal drug for the treatment of arterial hypertension continues. The most potent agents available until recently were the ganglion-blocking agents; these, although effective in reducing blood pressure, had disadvantages from the production of undesirable side effects due to parasympathetic blockade. A new drug, guanethidine ("Ismelin", Ciba) prepared by Mull and associates (Maxwell, Mull and Plummer, 1959) was found to inhibit sympathetic reflexes in the animal without affecting parasympathetic reflexes. We received a supply of this drug in 1959, and demonstrated that this selective action on the sympathetic nervous system also occurred in man, and that, over a short period of a few months, the drug was effective in controlling hypertension (Barnett, *et alii*, 1960).

In this paper we report a more extensive trial, based on our experience with its use in 32 patients who commenced treatment six months or more before December 1, 1960, and assess its place in the treatment of severe hypertension.

Material and Methods.

Subjects.

The patients comprised 29 who were attending our hypertension clinic, and who had previously been treated with ganglion-blocking drugs over periods ranging from six months to nine years, and three new patients not treated with these drugs (Table I). Their ages ranged from 36 to 61 years. There were 17 males and 15 females. All patients had suffered from severe hypertension when first presenting themselves for treatment, and papilœdema had been present in six. However, in the patients previously attending the clinic, blood pressure control was usually fairly good with treatment which included ganglion-blocking agents augmented by other drugs such as reserpine, chlorothiazide and hydralazine.

Dosage Schedule.

Our early studies had indicated that 100 mg. per day was a suitable dose to obtain a hypotensive effect after about two weeks, and the first eight patients received this dose for two weeks, with subsequent adjustment in

an attempt to achieve a maintenance effect. Advice from the makers indicated that this dose might be excessively large, and we decided that in patients treated subsequently we would use two dose schedules, an initial "high" of 75 mg. per day and an initial "low" of 30 mg. per day. Eleven patients received 75 mg. per day, 10 received 30 mg. per day and three received 50 mg. per day. The drug was supplied in tablets of 25 mg. and 10 mg., and was given as a single dose in the morning. In six cases the ganglion-blocking drug was suspended two days before a start was made with guanethidine, to demonstrate that a rise in blood pressure to hypertensive levels occurred without this treatment. In subsequent cases it was not considered justifiable to leave the patient without the protection of a potent hypotensive drug, and ganglion-blocking drugs were continued up to the commencement of guanethidine therapy and then reduced to zero over the next week.

General Management.

The first eight patients were admitted to hospital for the first two to three weeks of treatment. Subsequently most patients were treated as out-patients. Attendance was weekly during the early stages and later fortnightly. At each visit the systolic and diastolic blood pressures were measured with the patient lying, sitting and standing, symptoms and side effects were recorded, the patient was weighed and the urine was tested for albumin.

Toxicity Tests.

To determine whether there were any toxic effects on the kidneys, an estimation of the fasting blood urea level and the urinary protein excretion was made before treatment was begun, and then at intervals of one month. A full blood examination and liver function tests were performed before treatment was commenced and at intervals of three months.

Results.

Duration of Treatment.

This report is based on patients commencing treatment before June 1, 1960, and is compiled on results at December 1, 1960. All patients therefore had a possibility of six months' treatment, which was stopped only for some urgent reason. The duration of treatment is shown below:

Over 12 months	7 (one stopped)
9 to 12 months	3 (one died)
6 to 9 months	15
Under 6 months	7 (all stopped)

It will be noticed that the indications for stopping treatment (to be discussed later) were usually apparent before six months.

Blood Pressure Control.

In general, control of the blood pressure of patients treated with guanethidine was similar to that achieved with ganglion-blocking drugs. Of 25 patients treated for more than six months, 21 had been treated previously with ganglion-blocking drugs. Their blood pressure control was assessed by averaging the last four readings on each treatment. In nine cases there was no significant difference, in five the blood pressure was lower on guanethidine therapy, and in seven it was lower on ganglion-blocking drugs. Postural hypotension was of similar degree with the two treatments.

Side Effects.

Postural faintness occurred in about half of the patients, the incidence of this symptom being much the same as in treatment with ganglion blocking drugs. Diarrhœa also occurred in approximately half (18 of the 32). It was usually mild and controlled with propantheline, but was occasionally severe, and in one case was the reason for stopping treatment. Excessive tiredness and weakness were fairly common complaints (17 out of 32), and were the reason for stopping the drug in one case. When questioned on the matter, most of the male patients stated that they had noticed impaired ejaculation, but this was not a matter for complaint and was preferable to decreased potency during treatment with ganglion-blocking drugs. One patient complained of pain over the parotid glands.

Toxic Effects.

Full blood examination and liver function tests did not reveal any toxic effects on the blood-forming organs or on the liver.

A rise in blood urea level of more than 15 mg. per 100 ml. over the highest level recorded in the past 12 months was noted in nine cases (Table II). In six the rise was observed within the first six months of treatment, in three after the first six months. In one case the blood urea level, which had risen during the first six months of treatment, has since returned to the pre-treatment level in spite of the fact that the drug has been continued. Two of the patients with an increase in the blood urea level during treatment also showed for the first time the appearance of albumin in the urine at a level of more than 30 mg. per 100 ml. Albuminuria was also noted in a third patient not showing a rise in blood urea level.

We were unable to relate the rise in blood urea level to the blood pressure control, the previous renal status or to the dosage of guanethidine.

Reasons for Stopping Treatment.

In one case (Case 12), treatment with guanethidine was suspended for several weeks after a drop in blood pressure consequent on cardiac infarction. The blood pressure has since risen, and treatment has been recommenced.

Treatment has been permanently discontinued in another eight cases for the reasons listed below:

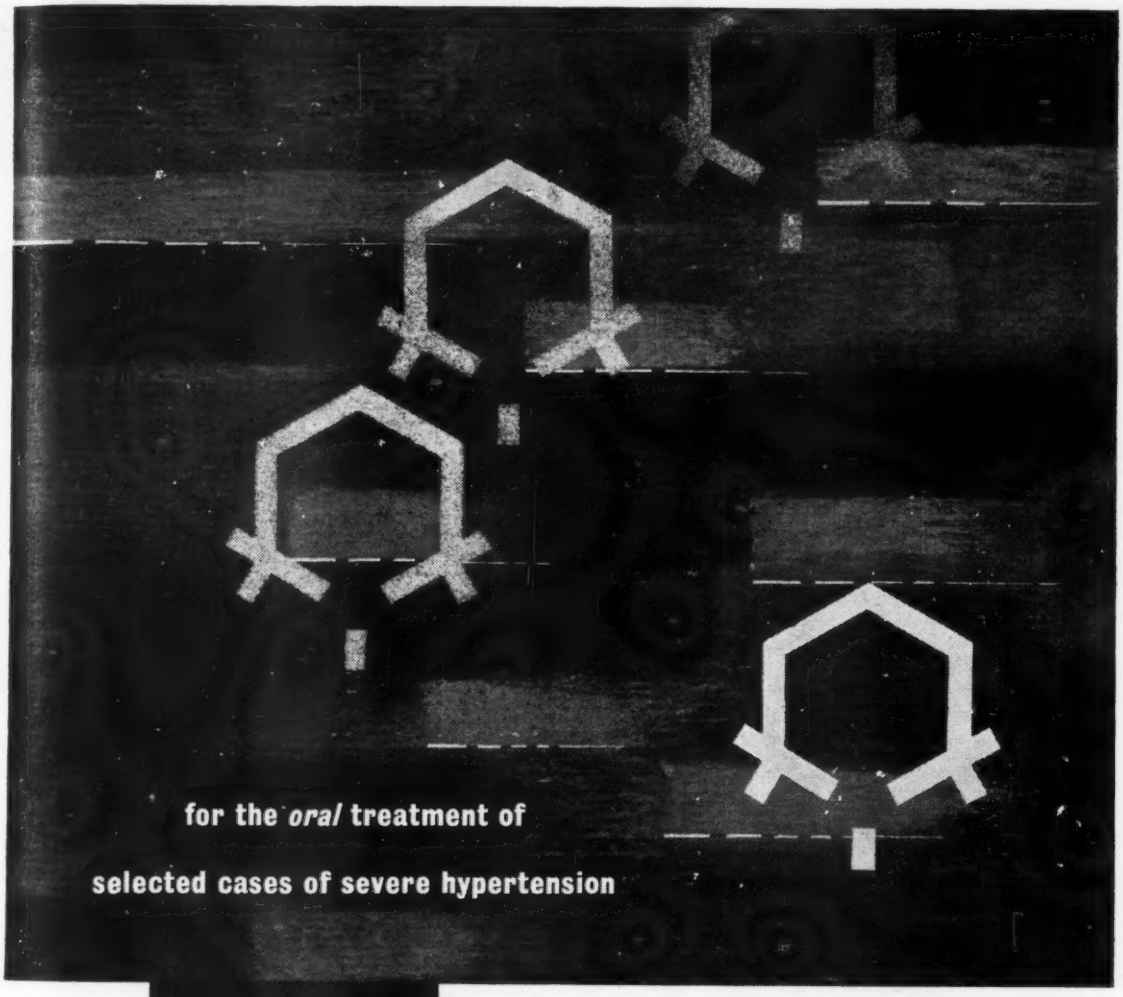
Excessive response	1
Lack of control of blood pressure with a dose of 100 mg. per day	3
Intolerable side effects (tiredness, shortness of breath, diarrhœa)	2
Refusal to continue the drug after abdominal pain	1
Persistently raised blood urea level	1

Apart from the patient with a raised blood urea level, all these patients had been treated for less than six months. Six of the cases must be regarded as treatment failures, in that blood pressure control could not be achieved without exceeding what was considered a reasonable dose, or without intolerable side effects.

Requisite Dose.

For convenience we have divided the patients into two groups with respect to initial dose — "high", 75 mg. per day or over, and "low", 50 mg. per day or lower, but usually 30 mg. per day. Twenty-one patients received initial high dosage. In three of these, blood pressure was not controlled in two to four weeks in spite of increasing the daily dose to 100 mg., and treatment with ganglion-blocking drugs was therefore resumed. In the other 18, satisfactory blood pressure control was obtained within two weeks. Of the 11 patients who received initial low dose treatment, blood pressure control was satisfactory within two weeks in eight, within three weeks in two, and within six weeks in one.

In 25 patients treated for more than six months, the early maintenance dose ranged from 30 to 70 (average 43) mg. per day, and the late maintenance dose from 15 to 175 (average 50) mg. per day. In four cases there was a late increase in dose of more than 50% above the early maintenance dose. Further information relating to the blood pressures and treatment of these patients is summarized below (Table III). In Case 8, the patient was a somewhat irregular attender, and it is doubtful



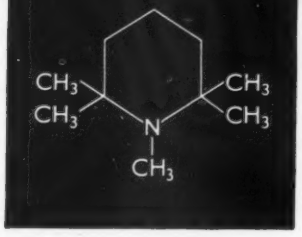


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TABLE I.

Summary of Results of Treatment with Guanethidine.

Case Number.	Patient's Sex and Age. (Years.)	Initial Phase.	Duration of Treatment with Ganglion-Blocking Drugs. (Years.)	Guanethidine Treatment. Duration. (Months).	Initial Dose (mg. per Day).	Early Maintenance Dose (mg. per Day).	Late Maintenance Dose (mg. per Day).	Blood Pressures (mm. of Mercury).[1] During Ganglion-Blocking Drug Treatment. Lying.	Standing.	During Guanethidine Treatment. Lying.	Standing.	Comment.
1	M.: 46	Malignant.	5	14	100	30	25	180/110	137/96	167/102	133/95	
2	M.: 47	Malignant.	8½	13	100	50	95	198/122	173/110	155/100	125/85	
3	M.: 46	Malignant.	7	13	100	50	35	175/115	132/91	179/110	155/100	
4	M.: 44	Malignant.	7	10	100	40	60	165/110	145/103	184/111	151/96	Died "suddenly".
5	M.: 43	Malignant.	6½	13	100	50	50	170/110	135/92	166/102	125/86	
6	M.: 53	Malignant.	7	12	100	50	50	173/112	136/96	176/92	115/82	Drug stopped because of rise in blood urea level.
7	M.: 52	Benign.	—	12	100	50	25	—	—	152/95	132/82	
8	F.: 36	Benign.	—	12	100	50	100	—	—	161/101	130/92	
9	F.: 48	Benign.	—	9	50	20	20	—	—	172/92	147/85	
10	F.: 55	Benign.	3½	9	30	40	70	138/92	102/78	171/110	146/87	
11	F.: 46	Benign.	8	8½	30	30	50	139/92	126/80	178/100	162/99	
12	M.: 42	Benign.	1½	7	75	—	75	178/115	162/113	178/116	166/109	Treatment suspended after cardiac infarction.
13	M.: 42	Benign.	½	8½	75	70	50	165/102	138/95	170/108	122/95	
14	F.: 54	Benign.	2½	8	30	30	20	130/85	105/76	135/79	120/80	
15	M.: 41	Benign.	7	8	30	50	40	155/103	165/108	145/95	136/94	
16	F.: 51	Benign.	4½	2 (8)[2]	30	—	—	165/95	158/105	160/95	165/95	Drug stopped because of side effects.
17	F.: 64	Benign.	7	1 (8)	75	—	—	162/93	148/90	220/98	248/110	Drug stopped because of failure to control hypertension.
18	F.: 69	Benign.	2½	8	75	50	175	177/104	187/118	195/120	192/120	
19	F.: 50	Benign.	½	1 (8)	75	—	—	170/115	127/96	157/97	143/97	Drug stopped because of side effect.
20	M.: 44	Benign.	1	1 (8)	75	—	—	162/100	160/98	180/120	170/110	Drug stopped because of failure to control hypertension.
21	M.: 50	Benign.	1½	8	30	30	25	150/94	127/89	185/99	156/102	
22	F.: 57	Benign.	4	1 (8)	30	—	—	113/87	102/83	90/80	100/90	Drug stopped because of excessive fall in blood pressure.
23	M.: 42	Benign.	2½	8	75	50	40	144/98	139/95	140/95	135/95	
24	M.: 60	Benign.	1	8	30	30	25	195/110	150/100	173/100	155/92	
25	F.: 43	Benign.	1	8	75	75	50	146/90	132/90	187/119	164/110	
26	M.: 59	Benign.	6	8	75	50	15	168/98	130/81	190/100	168/98	
27	F.: 57	Benign.	8½	½ (8)	75	—	—	170/108	156/102	230/140	230/140	Drug stopped because of failure to control hypertension.
28	F.: 55	Benign.	1	7½	75	50	50	154/102	140/92	154/101	148/96	
29	M.: 39	Benign.	2	7	30	30	40	155/97	142/92	158/105	151/99	
30	F.: 50	Benign.	3	6½	50	75	75	147/90	140/86	188/102	182/100	
31	F.: 49	Benign.	9	6½	30	60	50	166/92	136/88	207/115	186/106	
32	M.: 50	Benign.	1½	3 (8)	30	25	20	152/102	150/108	158/110	170/110	Drug stopped because of abdominal pain.

[1] Blood pressures are the average of the last four readings on the respective drugs, except for patients who stopped treatment in less than three months when the values just before stopping treatment are given.

[2] "8"—treatment stopped.

whether she always took all the tablets ordered. In Case 10, the blood pressure was fairly well controlled throughout, and it is doubtful whether the increase in dose was really necessary. However, in Cases 2 and 18, there was an escape from control of blood pressures about the seventh and sixth months respectively, leading to the prescription of a larger dose of guanethidine. It was still not adequately controlled after the dose had been increased, and addition of other drugs became necessary.

Discussion.

Although guanethidine has been available only for some 18 months, there have been numerous reports from American and European centres of its clinical use for periods ranging from a few weeks to 11 months (Page and Dustan, 1959; Richardson and Wyso, 1959; Frohlich and Freis, 1959, 1960; Leishman *et alii*, 1959; Jacquerod and Spuhler, 1960; Arnold and Kaiser, 1959; Leishman, 1960; Meesman, 1960; Lichtlen *et alii*, 1960; Richardson and Stephenson, 1960; Cottier *et alii*, 1960; Hege, 1960; Brest *et alii*, 1960; Gross, 1960; Dollery *et alii*, 1960; Evanson and Sears, 1960; Imhof *et alii*, 1960; Richardson and Magee, 1960; Genest, 1960; Clark *et alii*, 1960; Ford and Fallis, 1960; Perry and Camel, 1960; Brust *et alii*, 1960; Eagan and Orgain, 1960; Brest and Moyer, 1960; Finnerty *et alii*, 1960; Corcoran and Loyke, 1960). Although there have been minor differences, the results in general are consistent, in that guanethidine produces a hypotensive effect in the majority of patients, with side effects (particularly postural faintness) due to inhibition of sympathetic reflexes, but without the side effects (such as lack of accommodation for near vision, and constipation) due to inhibition of parasympathetic activity. The dose for individual patients has varied enormously, ranging from five to 750 mg. per day, but most patients have required between 25 and 125 mg. per day, with an average fairly consistently between 50 and 75 mg. per day. Details of administration have also varied, although most investigators have found once-daily administration satisfactory.

Some (for example, Richardson and Magee, 1960) have used a fairly large initial dose of 150 to 200 mg. per day, usually reduced later; others (for example, Leishman *et alii*, 1959) have preferred to start with a small test dose of 30 mg. per day, with cautious changes of only 10 mg. per day at weekly intervals as required. We have used both a moderately high initial dose and a low initial dose, and the final results have been much the same in both groups. Our average maintenance dose of 50 mg. per day is in line with that of most other workers. However, the range of dose used is rather less because, with one exception, we have not persisted with a dose above 100 mg. per day. In general, our results have been in accord with those of other workers, in that in the majority of cases it has been possible to achieve blood-pressure control comparable with that obtained with the ganglion-blocking drugs, but without those side effects due to parasympathetic blockade — lack of accommodation for near vision, dryness of mouth, constipation and impotence.

TABLE II.

Details Relating to Patients Showing a Rise in Blood Urea Level (15 mg. per 100 ml. or more) during Treatment with Guanethidine.

Case No.	Patient's Age. (Years.)	Initial Phase.	Duration of Treatment with Ganglion-Blocking Agents. (Years.)	Blood Urea Level in 12 Months Prior to Guanethidine Therapy (mg. per 100 ml.)	Dose, Blood Urea Level Proteinuria.[1]	Treatment with Guanethidine. (Months.) 1	2	3	4	5	6	7	8	9	10	11	12	13	14
2	47	Malignant.	8½	85–70	Dose ..	100	100	50	50	50	50	70	80	120	100	85	95	25 (+pempidine)	
					B.U. ..		70		105	85		90	70		95	90	115	85	115
					Prot. ..				<30	—			40	40		<30	<30	<30	
3	46	Malignant.	7	50–40	Dose ..	100	90	90	50	40	50	70	50	50	50	75	50	35	
					B.U. ..		50		75	60		70	60		65		70		
					Prot. ..					<30		<30	<30		<30		<30	<30	
4	44	Malignant.	7	30–40	Dose ..	100	40	40	45	50	50	50	50	50	60				Died
					B.U. ..	60	65	60		60	55		75	80	60				
					Prot. ..		<30	<30	<30	70	<30	<30	<30	<30	80				
6	53	Malignant.	7	70–55	Dose ..	100	50	50	50	50	35	35	50	50	60	50			
					B.U. ..	55	70		80	70	—	65	70	95	90	85			
					Prot. ..	0	<30				70	70	<30	<30	<30	<30			
7	52	Benign.	—	40	Dose ..	100	25	35	35	35	35	35	35	35	25	20			
					B.U. ..							40	45	50	60	55			
					Prot. ..							<30	<30	<30	<30	<30			
9	48	Benign.	—	35	Dose ..	50–20	20	20	20	20	20	20	20	20					
					B.U. ..	45			50			40	65						
					Prot. ..				<30			<30	<30						
10	55	Benign.	3½	50–60	Dose ..	30	40	50	60	70	70	70	70	70					
					B.U. ..		75		65	80			95						
					Prot. ..		40	<30	<30				0						
15	41	Benign.	7	40–40	Dose. ..	30–40	50	50	50	50	40	60	60						
					B.U. ..	45	40	40	50	50	60	45	40						
					Prot. ..	<30	<30	0	<30	<30	—	<30	<30						
32	50	Benign.	2½	20–30	Dose ..	75	25	25	—	—									
					B.U. ..	45	50	35		50									
					Prot. ..	<30	<30	<30		<30									

[1] Dose in mg. per day; B.U. blood urea level in mg. per 100 ml.; Prot., urinary protein excretion in mg. per 100 ml.

TABLE III.

Data Concerning Patients with Possible Development of Tolerance.

Case Number; Details of Patient.	Duration of Treatment. (Months.)	Blood Pressure (mm. of Mercury). Lying.	Standing.	Drugs Ordered. Guanethidine (mg. per Day).	Chlorothiazide (Grammes per Day).	Reserpine (mg. per Day).	Pempidine (mg. per Day).	Hydralazine (mg. per Day).
2. Man, aged 47 years, who presented initially in malignant phase. Treated with ganglion-blocking and other drugs for 8½ years.	2	195/120	140/98	50	—	—	—	—
	3	210/118	170/115	50	—	0·375	—	—
	4	190/112	152/102	50	—	0·375	—	—
	5	170/100	150/100	50	—	0·375	—	—
	6	140/100	140/90	50	—	0·375	—	—
	7	210/125	150/110	50	—	0·375	—	—
	8	220/130	200/120	70	—	0·375	—	—
	8½	230/120	190/120	100	—	0·375	—	—
	9	210/130	160/110	120	1	0·75	—	—
	10	130/90	90/60	75	1	0·75	—	—
8. Woman, aged 36 years, presented in benign phase. No previous hypotensive treatment.	1	220/120	150/110	75	—			—
	2	210/110	140/96	50	—			30
	3	200/118	160/114	40	—			60
	4	200/120	150/100	75	—			150
				In hospital with lupoid rash.				
	5	144/86	108/80	30	—			60
	6			Did not attend.				
	7	230/140	210/140	100	1			150
	7½	250/150	210/140	150	1			150
	8	200/116	190/110	250	1			150
	9	180/120	150/108	200	1			150
	10	170/94	120/82	100	1			150
	11	150/100	130/90	100	1			150
10. Woman, aged 55 years, presented in benign phase. Treated with ganglion-blocking drugs for 3½ years. Symptomatically well, but moderately impaired renal function (blood urea level 60 mg. per 100 ml.)	1	180/110	130/90	30	0·5			
	2	180/105	125/85	40	0·5			
	3	130/100	160/100	50	0·5			
	4	165/100	180/100	60	0·5			
	5	165/110	130/85	70	0·5			
	6	180/110	150/90	70	0·5			
	7	170/110	145/85	60	0·5			
	8	170/110	140/90	70	0·5			
	9	130/85	120/80	70	0·5			
18. Woman, aged 69 years, treated with ganglion-blocking drugs for 2½ years. Marked cardiac enlargement and auricular fibrillation. Main symptoms, dyspnœa and angina pectoris.	1	180/110	180/110	50	1		—	—
	2	170/110	160/115	50	1		—	—
	3	210/120	190/110	50	1		—	—
	3½	180/120	180/110	75	1		—	—
	4	180/120	150/100	75	1		—	—
	5	190/120	180/120	75	1		—	—
	5½	230/150	220/140	100	1		—	120
	6	200/130	220/120	150	1		—	—
	6½	200/120	180/120	175	1		—	—
	6½	200/120	190/120	50	1		7·5	—

Postural faintness has occurred with equal severity and frequency with both drugs. There have been certain side effects peculiar to the new treatment — diarrhœa, muscular weakness and tiredness, and impaired ejaculation — but most patients considered these less burdensome than those due to parasympathetic blockade and preferred the new treatment.

Tolerance was not a prominent feature, as indicated by the fact that the late maintenance dose of 50 mg. per day differed little from the early maintenance dose of 43 mg. per day. This presents no significant advantage over the modern ganglion-blocking drugs, in which any tolerance develops early and the patients are usually stabilized on a steady dose within a few weeks. However, it presents a distinct advantage over bretylium, to which tolerance is common and increases progressively over a period of months, so that it often proves impossible to obtain blood pressure control, even with large doses. However, some tolerance may occur in some cases, necessitating a larger dose of guanethidine or the administration of an additional drug. Tolerance is either not mentioned or stated to be absent in most of the reports. However, tolerance apparently occurred in one case in the series reported by Clark *et alii* (1960) and Ford and Fallis (1960) comment on the increased average maintenance dose (from 57 to 78 mg. per day) in their cases, occurring over a period of several weeks. It seems that, although a degree of tolerance may develop in some cases, this is not common and does not usually present a problem in management.

Our series included six treatment failures, which is a higher proportion than in most series. In three cases, there was inability to control the blood pressure with 100 mg. per day. It might have been possible to obtain a response with a higher dose; but with the information available at the time we were afraid of possible toxic effects, and were not inclined to leave our patients with uncontrolled hypertension while the appropriate doses were being determined, probably over a period of several weeks. In three cases, blood pressure could not be controlled without a dose producing side effects considered intolerable by the patients. They were subsequently treated satisfactorily with ganglion-blocking agents. Lack of response to guanethidine in occasional cases has been reported by other authors (Leishman, 1960; Hege, 1960; Brest and Moyer, 1960; Evanson and Sears, 1960; Frohlich and Freis, 1960). Conversely, guanethidine has been found of value for certain patients not responding to other therapy (Clark *et alii*, 1960; Perry and Camel, 1960).

A somewhat disturbing feature was a rise in blood urea level in a high proportion of our patients (nine of 25 treated for more than three months). Albuminuria of moderate degree appeared in three cases, but was inconstant and of doubtful significance. Microscopic examination of the urine showed no abnormality. Renal clearance studies after both oral medication (Richardson and Stephenson 1960) and intravenous administration (Bartorelli *et alii*, 1960; Mertz, 1960) have shown a decrease in the glomerular filtration rate (inulin clearance) and effective renal plasma flow (P.A.H. clearance) similar in nature to that occurring with treatment with ganglion-blocking drugs. Other workers (Richardson and Stephenson, 1960; Lichtlen *et alii*, 1960; Ford and Fallis, 1960; Kirkendall *et alii*, 1960; Leishman *et alii*, 1959), have recorded a rise in blood urea level, although most do not seem to have been very concerned about it. In the series treated by Ford and Fallis (1960), the average blood urea nitrogen level rose by as much as 100%. However, the serum creatinine level showed little change, and they deduced from this that the rise in blood urea level was not due to renal impairment. Kirkendall *et alii* (1960) considered a rising blood urea level the reason for stopping the treatment in one case. Seven patients in their series died, and necropsies were performed on five. They state that there were no unusual findings indicating renal damage from the drug; but it is not apparent whether these subjects include those with a rise in blood urea level following treatment. The cause of the rise in blood urea level is still not clear. It is unlikely to be due to the natural course of the disease, as seven of our nine patients had been under observation in the hypertension clinic for several years, during which time there had been no change in their renal status, and their blood urea levels had shown little change over the 12 months prior to commencing guanethidine therapy. In three cases the blood pressure control was somewhat better with guanethidine than with ganglion-blocking drugs, and in the others there was little difference (judged by clinical records) between the responses to the two treatments, although it is probable that the blood pressure (and renal blood flow) was more constantly reduced by guanethidine. If the rise in blood urea level is a reflection of better blood pressure control, one may expect it to fall if the patient reverts to his previous treatment. The subject needs further investigation. Meanwhile it would seem prudent to keep a close watch on the blood urea level of patients under treatment, and to stop it if there is a progressive rise.

Summary.

1. The results of the use of guanethidine for periods up to 14 months in treatment of 32 patients with severe hypertension are described.

2. There were six treatment failures, due to intolerable side effects in three cases, and to failure to control blood pressure with a dose of 100 mg. per day in three cases.

3. In the remaining cases, blood pressure control comparable with that from ganglion-blocking drugs was achieved, but with less severe side effects.

4. Side effects from parasympathetic blockade were absent. The side effects from guanethidine included postural faintness, diarrhœa, tiredness and weakness, each of which was noticed in about half the patients treated.

5. There was little difference in results obtained by starting with a high initial dose (100 mg. per day) or a low initial dose (30 mg. per day). The early maintenance dose of 43 mg. per day was not greatly different from the late maintenance dose of 50 mg. per day, indicating that tolerance was not a common feature. However, a degree of tolerance probably developed in two cases and possibly in two other cases.

6. A rise in blood urea level of at least 15 mg. per 100 ml. occurred in nine cases. The cause of this is obscure.

Conclusion.

Although guanethidine is not the ideal hypotensive drug and is not effective in all cases, it represents a distinct advance in the therapy of hypertension, in that inhibition of sympathetic activity can be achieved without the troublesome side effects of parasympathetic blockade. Pending the results of further observations, a close watch should be kept on the blood urea level during its use.

Acknowledgements.

We wish to thank the Ciba Company of Australia Proprietary Limited for the gift of the guanethidine ("Ismelin") used in this trial, and Dr. V. G. Balmer, Medical Director of this company, for keeping us supplied with the relevant bibliography.

References.

ARNOLD, O. H., and KAISER, K. (1960), *"Die Behandlung schwere Formen von arterieller Hypertonie mit Guanethidin"*, *Dtsch. med. Wschr.*, 85: 1236.

BARNETT, A. J., KINCAID-SMITH, P., and SIMPSON, F. O. (1960), "Observations on a New Hypotensive Drug: Guanethidine ('Ismelin')", MED. J. AUST., 2: 617.

BARTORELLI, C., GARGANO, N., REGOLI, D., and ZANCHETTI, A. (1960), *"Die Wirkung langdauernder Guanethidin-Verabreichung auf die Nierenfunktion von Hochdrukkranken"*, *Dtsch. med. Wschr.*, 85: 1271.

BREST, A. N., DUARTE, C., GLANTZ, G., and MOYER, J. H. (1960), "Preliminary Observations on the Antihypertensive Properties of Guanethidine", *Curr. Thera. Res.*, 2: 17.

BREST, A. N., and MOYER, J. H. (1960), "Therapeutic Use of Guanethidine in Hypertension", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 89.

BRUST, A. A., KING, L. R., and WITHROW, L. Z. (1960), "Effects of Guanethidine in Patients with Severe Hypertension", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 78.

CLARK, G. M., EDMONSON, J., and LEFKOVITS, A. (1960), "Clinical Report on Guanethidine — Treatment of Severe Diastolic Hypertension", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 58.

CORCORAN, A. C., and LOYKE, H. F. (1960), "Orienting Experiences with Guanethidine", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 117.

COTTIER, P., REUBI, F., and DUPASQUIER, E. (1960), *"Die Wirkung von Guanethidin auf den Hochdruck und die Nierenfunktion bei klinischer und ambulanter Behandlung", Dtsch. med. Wschr.*, 85: 1263.

DOLLERY, C. T., EMSLIE-SMITH, D., and MILNE, M. D. (1960), "Clinical and Pharmacological Studies with Guanethidine in the Treatment of Hypertension", *Lancet*, 2: 381.

EAGAN, J. T., and ORGAIN, E. S. (1960), "Side Effects of Guanethidine", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 83.

EVANSON, J. M., and SEARS, H. T. N. (1960), "Comparison of Bretylium Tosylate with Guanethidine in the Treatment of Severe Hypertension", *Lancet*, 2: 387.

FINNERTY, F. A., CHUPKOVICH, V., and MERENDINO, J. (1960), "Preliminary Observation on Parenterally Administered Guanethidine on Patients with Severe Hypertension", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 96.

FORD, R. V., and FALLIS, N. (1960), "The Physiology of Guanethidine with Special Reference to Renal Function", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 61.

FROHLICH, E. D., and FREIS, E. D. (1959), "Clinical Trial of Guanethidine, a New Type of Antihypertensive Agent", *Med. Ann. Dist. Columbia*, 28: 419.

FROHLICH, E. D., and FREIS, E. D. (1960), "Clinical Evaluation of Guanethidine — a Post Ganglion Sympathetic Blocking Agent", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 30.

GENEST, J. (1960), "Studies of Guanethidine Administration in 28 Patients with Arterial Hypertension", in "The University of Tennessee College of Medicine' Symposium on Guanethidine (Ismelin®)", Ciba: 47.

GROSS, W. (1960), *"Klinische Untersuchungen mit Guanethidin bei Hypertonikern", Med. Welt.*, 24: 1318.

HEGE, H. (1960), *"Klinische Erfahrungen mit einer neuartigen blutdruckenkenden Substanz", Med. Klin.*, 55: 793.

IMHOF, P. R., LEWIS, R. C., PAGE, I. H., and DUSTAN, P. (1960), "Effects of Guanethidine on Arterial Pressure and Vasomotor Reflexes", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 24.

JAQUEROD, R., and SPUHLER, O. (1960), *"Zur Behandlung schwerer Hypertonien mit Guanethidin", Schweiz. med. Wschr.*, 5: 113.

KIRKENDALL, W. M., FITZ, A. M., VAN HECKE, D. C., WILSON, W. R., and ARMSTRONG, M. L. (1960), "Hemodynamic and Clinical Effects of Guanethidine", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 103.

LEIBHMAN, A. W. D. (1960), *"Die Hochdruckbehandlung mit Guanethidin", Dtsch. med. Wschr.*, 85: 1231.

LEIBHMAN, A. W. D., MATTHEWS, H. L., and SMITH, A. J. (1959), "Guanethidine: Hypotensive Drug with Prolonged Action", *Lancet*, 2: 1044.

LICHTLEN, P., SCHAUB, F., and BÜHLMANN, A. (1960), *"Klinische und experementelle Untersuchungen über die blutdrucksenkende Wirkung von Guanethidin", Dtsch. med. Wschr.*, 85: 1249.

MAXWELL, R. A., MULL, R. P., and PLUMMER, A. J. (1959), "[2 - (Octa hydro - 1 - azocinyl) - ethyl] - guanidine sulfate (Ciba 5864 - SU), A New Synthetic Antihypertensive Agent", *Experimentia*, 15: 367.

MESSMAN, W. (1960), *"Klinische Erfahrungen bei der Behandlung der arteriellen Hypertonie mit Guanethidin", Dtsch. med. Wschr.*, 85: 1243.

MERTE, D. P. (1960), *"Über die akute und protrahierte Wirkung von Guanethidin auf die Nierenhamodynamik, den Wasser und Elektrolythaushalt bei gesunden Personen", Dtsch. med. Wschr.*, 85: 1278.

PAGE, I. H., and DUSTAN, H. P. (1959), "A New Potent Antihypertensive Drug. Preliminary Study of [2 - (Octahydro - 1 - Azocinyl) - Ethyl] - Guanidine Sulfate (Guanethidine)", *J. Amer. med. Ass.*, 170: 1265.

PERRY, H. M., and CAMEL, G. H. (1960), "Guanethidine: Some Pharmacologic and Clinical Observations", in "The University of Tennessee College of Medicine Symposium on Guanethidine (Ismelin®)", Ciba: 69.

RICHARDSON, D. W., and MAGEE, J. H. (1960), "Influence of Guanethidine on Cardiac Output and Renal Function", in "The University of Tennessee College of Medicine, Symposium on Guanethidine (Ismelin®)", Ciba: 37.

RICHARDSON, D. W., and STEPHENSON, M. P. (1960), *"Über die Wirkung von Guanethidin auf den Blutdruck, das Herzzeitvolumen und die Nierenfunktion", Dtsch. med. Wschr.*, 85: 1258.

RICHARDSON, D. W., and WYSO, E. M. (1959), "Effective Reduction in Blood Pressure Without Ganglionic Blockade", *Va. med. Mon.*, 86: 377.

Addendum.

Since completing this trial, we have treated a few patients with a combination of guanethidine and the ganglion-blocking drug pempidine, with good blood pressure control and minimal side effects. Although in general one does not wish to use an unduly large number of drugs in one patient, this combination is useful in a minority of cases in which it is difficult to get adequate blood-pressure control without troublesome side effects. Thus diarrhœa from guanethidine is counteracted by the constipating effect of pempidine. Undue hypotension in heat waves can be corrected by reducing the dose of the short-acting pempidine without alteration in the dose of the long-acting guanethidine.

TREATMENT OF MALIGNANT DISEASE WITH AN ALKYLATING AGENT: REVIEW OF 100 PATIENTS TREATED WITH "ENDOXAN".

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AT present methods of treating advanced malignant disease are far from satisfactory. Attempts have been made to improve survival rates of patients with this condition by extending the scope of surgery, by increasing the power and range of machines for radiotherapy and by the use of "anti-cancer" drugs.

In this study, "Endoxan" (B518, "Cytoxan", cyclophosphamide — Figure I), an alkylating agent, has been used.

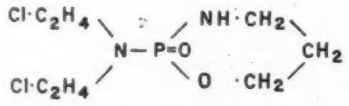

FIGURE I.

N, N-Bis(β-chlorethyl)-N', O-propylene-phosphoric ester-diamide ("Endoxan").

The biological effect of alkylating agents depends upon their capacity to prevent multiplication of rapidly dividing cells by disordering nucleoprotein synthesis and chromosomal duplication, thereby retarding or inhibiting cellular activity.

"Endoxan" was developed by Arnold and Bourseaux (Arnold *et alii*, 1958) in an attempt to increase the selectivity of cytotoxic drugs by the production of an inactive form which is subsequently transformed to the active compound after administration to the patient. It is one of a group of N-mustard-phosphoramides, which compounds act as substrates for phosphoramidases. These enzymes have been reported by Gomori (1948) to occur in tumour tissue at higher than normal levels; consequently it may be expected that maximal activation of the drug occurs at the tumour site.

[1] Senior surgical research officer working under a grant from the New South Wales State Cancer Council.

TABLE I.

Results of Treatment with "Endoxan" of 100 Patients with Advanced Malignant Disease.

Tumours.	Total Number of Patients Treated.	Death Within 16 Days of Treatment.	Regression.	Partial Regression.	Transient Regression.	Indeterminate Result.	Failure.
Lung:							
Anaplastic carcinoma	22	3	3	5	4	2	5
Squamous carcinoma	23	3	2	7	3	3	5
Adenocarcinoma	3	—	1	—	—	—	2
Brain:							
Metastasis from lung	4	—	—	1	3	—	—
Glioma	4	—	—	1	—	2	1
Gastro-intestinal:							
Colon	7	—	1	2	—	—	4
Stomach	5	—	—	4	—	—	1
Gall-bladder	1	1	—	—	—	—	—
Pancreas	2	2	—	—	—	—	—
Tongue	1	—	—	—	1	—	—
Jejunum (sarcoma)	1	—	—	—	1	—	—
Genito-urinary:							
Kidney (hypernephroma)	5	—	—	—	1	—	4
Ovary	2	—	—	—	1	—	1
Cervix		1	—	—	—	—	
Uterus		—	—	—	—	—	
Prostate	1	—	—	—	1	—	—
Testis (teratocarcinoma)	1	—	—	—	—	1	—
Penis	1	—	—	—	1	—	—
Miscellaneous:							
Breast	3	—	1	1	1	—	—
Thyroid	1	—	—	1	—	—	—
Melanoma	5	—	1	1	—	1	2
Mycosis fungoides	1	—	1	—	—	—	—
Lymphosarcoma (spine)	1	—	1	—	—	—	—
Neuroblastoma	1	—	1	—	—	—	—
Anaplastic carcinoma	2	—	—	1	1	—	—
Total	100	10	12	24	18	9	27

Arnold *et alii* (1958) have studied the effect of "Endoxan" in rats with Yoshida ascites sarcoma, Walker carcinoma and Jensen sarcoma. They found it to have a high therapeutic index (good antitumour effect and low toxicity) and to effect a cure in a high percentage of rats with these tumours. Some authors have suggested that the drug has a significantly higher therapeutic index than that of other alkylating agents (Brock and Wilmanns, 1958), while others (Foye, 1960; Papac, 1960) state that it has about the same antitumour effect as other alkylating agents. It is agreed that the ease and versatility of its administration, combined with its relatively low toxicity to bone marrow, make it a valuable chemotherapeutic agent (Papac *et alii*, 1960; Foye *et alii*, 1960; Haar *et alii*, 1960).

Methods.

The patients treated were those who were not considered suitable subjects for radiation therapy or surgery. All patients had histologically proven malignant disease. One hundred patients with various types of malignant disease (Table I) were treated by single-dose technique on 136 occasions. In cases in which the patients were retreated, the interval between doses was a minimum of three weeks.

Hæmoglobin level estimations, white-cell counts, platelet counts, estimations of the serum uric acid and blood urea levels and "Bromsulphalein" retention tests were carried out prior to therapy and at intervals thereafter.

The method of treatment has been to administer maximal doses of the drug, because it is known that tumours develop resistance to alkylating agents (Karnofsky, 1958). It is believed that a single large dose or intermittent large doses may more effectively prevent tumour resistance than frequent small doses.

In this series 40 to 100 mg. per kilogram of body weight of "Endoxan" has been used. A dose of 40 to 50 mg. per kilogram has given the best results and would appear to be the optimal dose. The maximum single dose has never exceeded four grammes. However, this is far larger than the recommended dosage of 100 to 200 mg. per day to a total of four grammes. All patients were given 25 mg. of chlorpromazine by intramuscular injection to prevent nausea, and 100 mg. of pentobarbitone for sedation one hour prior to treatment. The drug was mixed by dissolving the contents of each ampoule containing 200 mg. of "Endoxan" in 5 ml. of water. It was then injected with a syringe into the tubing of an intravenous saline infusion apparatus just proximal to the needle. The tubing had been clamped off above the site of the injection, and after each injection the tubing was flushed with saline.

Results.

Ten patients died within 16 days of treatment, but in no instance was it believed that the drug was directly responsible for death, or that maximal benefit had been derived from the drug (Table I).

The response to treatment has been assessed from the change in tumour size and from the evidence of symptomatic relief, and has been classified as follows: (i) regression; (ii) partial regression; (iii) transient regression; (iv) indeterminate; and (v) failure (Table I). Regression denotes reduction of tumour size by 80% or more, as observed clinically or radiologically, combined with relief of symptoms and improvement in general well-being for two months or longer. Regression occurred in 12 cases.

Partial regression signifies a reduction of 40% or more in tumour size lasting for a month or more, associated with an appreciable degree of palliation of symptoms. Partial regression occurred in 24 cases.

Of the remaining patients, 18 showed transient regression — namely, evidence of reduction in tumour size for shorter periods, and relief of pain lasting from a few days to a few weeks. In nine cases no evidence of improvement was available and these were classified as indeterminate. Failure, represented by progression of the tumour, occurred in 27 cases.

The clinical response was frequently rapid and occasionally dramatic. An improvement in the state of well-being; an increase in appetite and a less frequent need of a narcotic were observed in 63 cases. The following case shows the symptomatic improvement that may occur.

A male, aged 75 years, with destruction of the eleventh and twelfth thoracic vertebræ by metastatic carcinoma of the lung, required half a grain of "Omnopon" every three to four hours prior to treatment. Twelve hours after treatment with "Endoxan", his pain was strikingly decreased, being controlled by aspirin and codein tablets in a dosage of two every four hours. His pain relief persisted until

three days prior to his death, which occurred four weeks later.

Clinical Effects of the Drug.

After the administration of "Endoxan" there were a number of effects on the patient; these were systemic, hæmatopoietic, alopecia and urinary symptoms.

Transient giddiness was observed for a few seconds after the commencement of administration, but passed off quite rapidly. Nausea and vomiting of varying severity occurred in 80% and diarrhœa occurred in 4% of cases during the 24 to 48 hours after injection of the drug, and these symptoms were frequently more severe when administration of the drug had to be repeated.

Severe leucopenia is usual eight to 12 days after the administration of "Endoxan" (Figures IV and V), but recovery has always occurred quite rapidly. The platelet

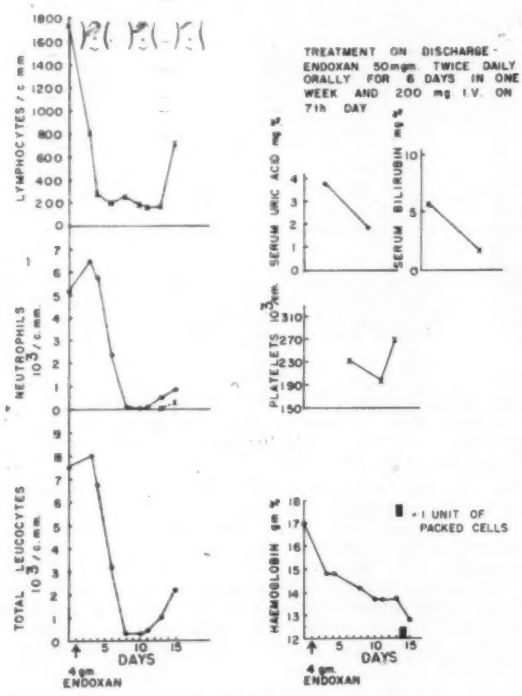

FIGURE IV.

count may fall a little, but in this series there has been evidence of a fall to low levels in two cases only. One patient developed purpuric spots on the legs and the other suffered a mild epistaxis.

The hæmoglobin level may fall several weeks after therapy and transfusion may be required.

In three cases septicæmia developed at the time of greatest white-cell depression. Each patient was treated with the appropriate antibiotic and all three recovered.

Alopecia of the head and face, but not of the axillæ or pubic region, develops in 60% of cases, and frequently 75% to 90% of the hair is lost, males having no need to shave. The hair commences to fall three to four weeks after the administration of the drug and grows again after three months. The new hair is thicker and often of a different colour, and does not fall as readily on further administration of the drug.

Hæmaturia occurs in 40% of cases for about 48 hours after the drug is given. Cystoscopic examination of severely affected patients has revealed florid bullous cystitis. Microscopic studies of the urine revealed red cells and epithelial cells, but casts have been seen on one occasion only. In four cases sterile cystitis persisted for approximately one month. The blood urea levels and "Bromsulphalein" retention were not affected by administration of the drug.

Reports of Cases.

A., a male, aged 61 years, had a radio-opaque mass in the left lung (Figure II).[1] A bronchoscopy, a biopsy and subsequent histological examination revealed an anaplastic carcinoma. Two weeks later the patient became jaundiced and developed palpable lymph nodes in the cervical region;

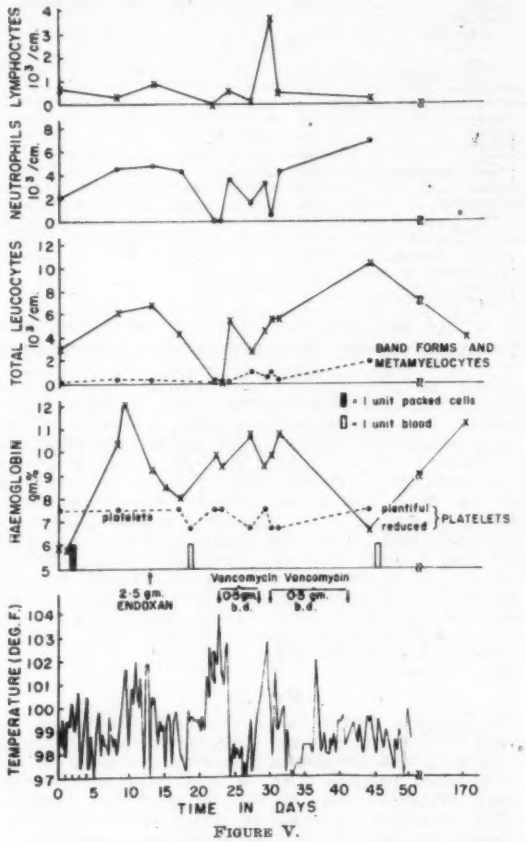

FIGURE V.

the liver was enlarged to be palpable 7 cm. below the costal margin, and he was severely ill. The patient was given four grammes of "Endoxan" (75 mg. per kilogram) intravenously. In 10 days his liver was reduced in size, being palpable 3·5 cm. below the costal margin (Figure IV), and his serum bilirubin level had returned to normal. The lymph nodes in his neck became impalpable. On the fifteenth day after injection he was discharged from hospital. Radiological examination of his chest showed improvement (Figure III) and his general sense of well-being had increased. He was maintained on oral administration of the drug (this method of therapy has now been discontinued). He died recently, nine months after his initial therapy, and was able to get about until six weeks prior to his death. His local medical adviser states: "It appears that this drug gave him approximately eight more months of life."

B., a female, aged 56 years, was admitted to hospital with a history of progressive paraplegia and anæmia, the latter necessitating the administration of one or two units of packed red cells per week. Three years previously she had undergone a small bowel resection for lymphosarcoma. One

[1] For Figures II and III see art-paper supplement.

year previously she was admitted to hospital with quadriplegia, and a decompressive laminectomy at the level of the eighth cervical vertebra was performed for metastases. This was followed by deep X-ray therapy. Movement and sensation in her arms and legs returned to a slight extent. However, some five months later these symptoms recurred. She also developed anæmia, requiring weekly transfusion of 200 to 400 ml. of packed red cells. She was unable to walk, sit up or write. She required an indwelling catheter, and a urinary tract infection was present. Her blood picture is recorded in Figure V. After a blood transfusion and control of her urinary infection, she was given 2·5 grammes (40 mg. per kilogram) of "Endoxan". Ten days after therapy the leucocyte count fell to 100 cells per cubic millimetre and the patient developed staphylococcal septicæmia; for this she was treated with vancomycin and she recovered. She also developed complete alopecia by the third week after treatment. However, after six weeks her anæmia abated, and she has now had no transfusion for six months. Thus, eight months after therapy she maintains a hæmoglobin level of 11·6 grammes per 100 ml., her hair has grown again, she is able to sit out in a chair and she has developed much more power in her arms and legs, being able to walk with help.

Discussion.

"Endoxan" is an alkylating agent, and is only one of many drugs of this type available for the treatment of malignant disease. Where its place amongst alkylating agents should be yet remains to be seen; however, in this study certain of its characteristics have been observed and show it to be a drug worthy of further study.

Effective relief of symptoms and an increased sense of well-being were observed, and 63 patients had relief from pain.

"Endoxan" has a low toxicity and, in particular, spares the platelets; hence it can be used in large doses at frequent intervals, and it is postulated that this method of treatment may have greater effect on malignant tumours.

Summary.

1. "Endoxan" is an alkylating agent which can be used in relatively high doses without severe bone-marrow depression, and its use in the treatment of 100 patients with malignant disease is reported.

2. The results with the drug appear to be similar to those reported for some other alkylating agents, but it is less toxic and therefore of greater therapeutic advantage.

3. Some tumour regression is observed in about one-third of patients. Ten *per centum* of patients have shown marked improvement, and have resumed normal activity for periods ranging from two to nine months.

4. Alopecia is an annoying side effect in 60% of cases, but results to date warrant further use of the drug.

Acknowledgements.

My thanks are due to my colleagues of the Unit of Clinical Investigation for their encouragement and assistance in preparing this paper. I am indebted to those members of the honorary and resident medical staffs of the Royal North Shore Hospital whose cooperation made the study possible. I am further indebted to Dr. G. L. Bennett, of Woodville, South Australia, for furnishing late details in the case of the patient A. Mr. Ian MacDonald of Charles MacDonald-Mead Johnson made generous supplies of "Endoxan" available during this study.

References.

ARNOLD, H., and BOURSEAUX, F. (1958), *"Synthese und Abbau cytostatisch wirksamer Zyklischer N-Phosphamid-ester des bis(β-Chloräthyl-amins"*, *Angewandte Chemie*, 17: 539.

ARNOLD, H., BOURSEAUX, F., and BROCK, N. (1958), *"Neuartige Krebs-Chemotherapeutika aus der Gruppe der Zyklischen N-Lost-phosphamidester"*, *Naturwissenschaften*, 45: 64.

BROCK, N., and WILMANNS, H. (1958), *"Wirkung eines Zyklischen N-Lost Phosphamidesters auf experimental erzeugte Tumoren der Ratte"*, *Dtsch. med. Wschr.*, 83: 453.

FOYE, L. V., CHAPMAN, C. G., WILLETT, F. M., and ADAMS, W. S. (1960), "Cyclophosphamide. A Preliminary Study of a New Alkylating Agent", *Cancer Chemotherapy Reports*, 6: 39.

HAAR, H. G., MARSHALL, J., BIERMAN, H. R., and STEINFIELD, J. C. (1960), "The Influence of Cyclophosphamide upon Neoplastic Diseases in Man", *Cancer Chemotherapy Reports*, 6: 41.

KARNOFSKY, D. A. (1958), "Summary of Results Obtained with Nitrogen Mustard in the Treatment of Neoplastic Disease", *Ann. N.Y. Acad. Sci.*, 68: 899.

PAPAC, R., PETRAKIS, N. L., AMINI, F., and WOOD, D. A. (1960), "Comparative Clinical Evaluation of Two Alkylating Agents", *J. Amer. med. Ass.*, 172: 1387.

Legends to Illustrations.

FIGURE II.—There is a large mass with irregular margins extending from the hilum of the left lung. The left hemidiaphragm is markedly elevated. The appearance is that of a bronchial neoplasm with involvement of the phrenic nerve.

FIGURE III.—Twelve days after the previous radiograph (Figure II) was taken, the lesion appears to be smaller.

THE SCOPE FOR RESEARCH IN GENERAL PRACTICE.[1]

By J. G. RADFORD, M.B., B.S., M.R.A.C.P.,
Chairman of Research Committee, Australian College of General Practitioners.

THE Concise Oxford Dictionary of English defines research as "careful search or inquiry after — endeavour to discover facts or the scientific study of a subject, a course of critical investigation".

This is a very broad definition. It can be narrowed by the addition of such qualifying words as "clinical" or "laboratory", with the implication that the study of disease is undertaken in hospital patients or laboratory material respectively. In popular imagery, research conjures up pictures of highly-equipped laboratories with white-coated workers devoting their full-time endeavours to the solution of academic problems. Even some members of our own profession labour under this delusion, but most of us realize that modern medical research also includes clinical research. Several of our larger hospitals have clinical research units devoted solely to this purpose. What many of us forget is that this concept can be extended still further to the study of patients in their own homes and in the family doctors' consulting rooms.

Research Fields for the General Practitioner.

This type of work can be carried on in parallel with the doctor's primary function of diagnosing and treating illness, just as it does in the clinical research units of the hospitals. In them patients receive diagnostic and therapeutic care as well as being the subjects of clinical research. However, they are a highly selected group, in that they gain admission to these units because they are suffering from certain complaints, frequently in their more serious forms, which are currently under investigation. The general practitioner, on the other hand, is dealing with the complete spectrum of disease. The only case selection is that conditioned by the type of area in which he practises, or occasionally by a personal interest or above-average competence in a particular field of work, for example, when the general practitioner cultivates a pædiatric or a geriatric type of practice. It is the general breadth of his work, and still more, the fact that he treats patients "from the cradle to the grave", that provides him with the ideal opportunity to study certain aspects of disease. Also he sees patients in the environment of their own homes, rather than in the somewhat artificial one of the hospital. He is working *in vivo*, not *in vitro*. One field wide open to

[1] Read at first Australian General Practitioners' Convention on October 13, 1960, at Melbourne.

him is the study of hereditary factors in the pathogenesis of disease.

If one were obliged to use an adjective to qualify the type of research he can do, it would probably be "observational". I do not altogether like this word, because careful observation enters into any type of research. I use it in the sense that the first thing a general practitioner researcher will do is observe carefully, then he will record and analyse his findings. From this point he may synthesize a hypothesis which must be tested in the usual scientific sequence. This is in contrast perhaps to the laboratory worker, who may begin with a hypothesis and then proceed to test its correctness.

Particular branches of this observational research in which the general practitioner can take part include studies in morbidity — that is, the frequency and severity of various diseases, their natural history and their prognosis. He is also in an ideal position to study the epidemiology of infectious diseases. In this he may need to work along with a health authority and the laboratory. This opens up the question of the general practitioner collaborating in a team with other workers — for example, laboratory technicians and the specialist scientist. This is a fruitful source of work. The general practitioner can collect material, the laboratory may be required to examine some of it and the scientist (including the statistician) may be best suited to carry out the ultimate analysis. An excellent example of this was the study of staphylococcal soft-tissue infections recently carried out by the Department of Health (National Health and Medical Research Council, 1960). Clinical data and specimens were collected by the general practitioner; culture and sensitivity tests were done in the laboratories; and the final analysis was carried out by the epidemiologists. Another type of work in which the family doctor can participate is therapeutic research. This I have deliberately left until last. The great difficulties of clinical trials are well known — for example, the importance of adequate criteria for assessing improvement and the comparison with an adequate control series. For ethical reasons it is doubtful if the general practitioner can use an inert preparation as a control. However, he can reassess the value of traditional methods of treatment, which are apt to be accepted blindly as infallible. He can also compare a new preparation, thought by the laboratory team to be efficacious, and proved to be non-toxic, with the traditional remedy. He can quite unwittingly find himself trying out remedies advertised on his blotting paper, or extolled by an enthusiastic traveller. Surely it is more reasonable for him to test new drugs in a scientific manner as part of an organized programme?

Historical.

Having mentioned already in some detail in what type of work the general practitioner can participate, I shall briefly deal with one or two historical references. Firstly, I would remind you that it was a general practitioner in Sudbury, Gloucestershire, who realized the clinical significance of the remark made by the dairymaid: "I've had the cowpox and girls who have had the cowpox cannot take the smallpox." Even if Edward Jenner plagiarized from the dairymaid, his realization of the significance of her remark has saved many lives. Next, I would mention the fact that James Mackenzie wrote emphatically on the advantages of general practice as a medium for research. It was he who stressed the fact that the general practitioner sees disease in its true prospective from the early symptoms to the end (Pickles, 1939). Finally, I would remind you of the brilliant epidemiological work done by a general practitioner in the Wensleydale district of Yorkshire. I refer, of course, to William Pickles, whose monograph on epidemiology in country practice should be compulsory reading for all students and general practitioners.

General-Practice Research in the Past Decade.

I shall now refer to some of the ways in which the College of General Practitioners in Britain has fostered research in general practice. The College has realized that there are various levels at which this work can be carried out. Firstly, a single-handed worker can observe and record his observations in a subject in which he is especially interested. Here he needs mostly encouragement and advice. Secondly, a group of workers interested in a particular subject may band together and pool their case material and their thoughts. Here the College, through its research register and its committees, can bring these people together. It can also provide means for the analysis of the data obtained. Finally, when a smaller amount of information is required from a larger number of people, it can approach all its members for information on a wider scale.

As an example of a single-practitioner study, I would quote that of Dr. John Fry, who carefully studied the 1957 influenza epidemic in his own practice in an outer London suburb (Fry, 1958). He investigated, *inter alia*, the age-distribution of his patients and the incidence of chest complications in the various groups.

To illustrate an example of a group study, I would quote the "Survey of Epilepsies in General Practice" by a group of 134 workers organized by Dr. C. A. H. Watts (College of General Practitioners, 1960). It was estimated that between four and five persons per thousand in England and Wales were suffering from epilepsy, most commonly between the ages of 15 and 24 years. First fits were most common in the first two years of life. Watts estimated that for every first fit, one case in eight will go on to become a chronic epileptic. He also carefully analysed the social and employment problems attendant on the diagnosis of epilepsy.

Next, as an example of a large group study, I shall mention the morbidity study carried out in 1955 and 1956 by the College of General Practitioners in conjunction with the General Register Office (Logan and Cushion 1958). This valuable monograph indicates the frequency of all diseases in the community as a whole and gives some idea of the invalidism caused thereby.

On a somewhat different line is the work carried out by Dr. G. I. Watson in the Epidemic Observation Unit of the College. When a member notifies the occurrence of an unusual epidemic, the "spotters" all over England are alerted and sent a brief description of the syndrome. They are asked to report diagnosed cases (including "nil returns") and to obtain material for analysis by virus laboratories. Most interesting information is being obtained regarding the clinical syndromes produced by some of the more recently identified viruses such as the Coxsackie and ECHO groups. One such epidemic, localized to the Midlands, caused a syndrome in children characterized by stomatitis and a peripheral macular eruption. It proved to be due to a Coxsackie (Group B) virus.

I have described elsewhere numerous examples of the research work done by the College of General Practitioners (Radford, 1960).

The Present Position of General-Practice Research in Australia.

We may now ask what has been done in this field in Australia. Work already completed by the Australian College of General Practitioners includes a survey of the incidence of eclampsia in New South Wales and Queensland (College of General Practitioners, 1956), a survey of allergic reactions to penicillin (Australian College of General Practitioners, 1959), a limited study of the penicillin sensitivity of *Staphylococcus aureus* in general practice (Australian College of General Practitioners, 1959) and a survey of anæmia in three general practices (Australian College of General Practitioners, 1960). I have already referred to the wider study of staphylococcal soft-tissue infections carried out by the National Health and Medical Research Council in cooperation with the general practitioners (National Health and Medical Research Council, 1960).

Another study in New South Wales, already completed, is awaiting publication (Australian College of General Practitioners, 1961). It comprises observations on infective hepatitis, in which 43 observers submitted histories of 289 cases. In Victoria studies on allergy to tetanus antitoxin and post-partum haemorrhage are completed. The results of the last four studies are awaiting publication. Several other studies are still in progress, including a "home-accident" survey in Western Australia and a project on asthma in childhood in Queensland.

With regard to future projects, the Australian College is at present doing preliminary studies in methods of morbidity-recording. In 1961 a pilot study on this subject is being carried out. Ultimately the College hopes to produce a complete picture of the incidence of, and morbidity from, various diseases seen in the whole of general practice. There are a number of works on mortality in this country and a limited amount of information concerning morbidity in hospitals. However, the over-all picture of morbidity outside the hospital sphere is, at the moment, a matter of conjecture only.

In the field of epidemiology, work has been commenced in New South Wales on the culture of viruses from various clinical syndromes. This work is continuing.

Conclusion.

I have attempted to present some of the ways in which the general practitioner can contribute to medical knowledge by observational research. Much that I have said concerns what has already been achieved and written, but I have indicated in what direction progress in this field in Australia is being directed.

References.

AUSTRALIAN COLLEGE OF GENERAL PRACTITIONERS, RESEARCH COMMITTEE (1959), "Report on a Survey on Allergic Reactions to Penicillin", recorded by N. A. Anderson, MED. J. AUST., 1: 827.

AUSTRALIAN COLLEGE OF GENERAL PRACTITIONERS, RESEARCH COMMITTEE (1959), "A Survey of the Penicillin Sensitivity of Staphylococcus Aureus in General Practice", recorded by W. Breinl, MED. J. AUST., 2: 355.

AUSTRALIAN COLLEGE OF GENERAL PRACTITIONERS, RESEARCH COMMITTEE (1960), "The Incidence of Anæmia in General Practice in New South Wales", recorded by R. D. Spooner, MED. J. AUST., 2: 727.

AUSTRALIAN COLLEGE OF GENERAL PRACTITIONERS, RESEARCH COMMITTEE (1961), "Observations on Infective Hepatitis in Australian General Practice", recorded by J. G. Radford, *Ann. gen. Pract.*, to be published.

COLLEGE OF GENERAL PRACTITIONERS, RESEARCH COMMITTEE (1956), "An Investigation into the Incidence of Eclampsia in General Practice in New South Wales and Queensland", MED. J. AUST., 1: 870.

COLLEGE OF GENERAL PRACTITIONERS, RESEARCH COMMITTEE (1960), "A Survey of the Epilepsies in General Practice", recorded by C. A. H. Watts, *Brit. med. J.*, 2: 416.

FRY, J. (1958), "Influenza A(Asian) 1957. Clinical and Epidemiological Features in a General Practice", *Brit. med. J.*, 1: 259.

LOGAN, W. P. D., and CUSHION, A. A. (1958), "Morbidity Statistics from General Practice", H.M.S.O., Studies on Medical and Population Subjects, Number 14.

NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL (1960), "A Survey of Staphylococcal Infections of the Skin and Subcutaneous Tissues in General Practice in Australia", Special Report Series, Number 10.

PICKLES, W. N. (1939), "Epidemiology in Country Practice", John Wright and Sons.

RADFORD, J. G. (1960), "Research in General Practice in Great Britain", *Bull. Post-Grad. Comm. Med. Univ. Sydney*, 16: 79.

INTERNAL FIXATION OF FRACTURES OF LONG BONES WITH METALLIC DEVICES.

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LAPEYODE AND SICRE wired fractured bones in 1775 and this kindled the search for metals that could be used to fix fractures internally. Arbuthnot Lane failed because his metal plates corroded despite his "no-touch" technique.

Stainless steel dates from a British patent taken out in 1913, and was the result of a special search for a metal that would make naval guns resistant to sea water. It was used successfully in the more peaceful application of the manufacture of Sheffield cutlery. Stainless steel has been thoroughly investigated for internal use, more usually by "turning others' pages" and repeating mistakes. We know that there are scores of alloys all called "stainless steel". The Fracture Committee of the American College of Surgeons is trying to protect the surgeon by laying down a rigid standard for metals, and it lists an 18/8 "S.Mo." stainless steel alloy which is non-irritating.

Venable and Stuck helped pioneer the use of vitallium, which was developed for dental use. It is more reliable than stainless steel, but it cannot be drawn; all vitallium appliances are cast. This renders difficult the manufacture of wires and long pins and is a disadvantage in certain circumstances.

The Physiology of Repair and Some Surgical Principles.

Mechanics.

The function of bone is rigidity, but bone is a living, dynamic organ, capable of adaptation and repair. Nature gives us tubes of compact bone which are stronger, weight for weight, than can be made of steel, so we should not be surprised when an 11 mm. stainless-steel intramedullary nail snaps without great effort when the ordinary forces of the body act on it.

Resorption.

Compact bone is a living mosaic of ground lamellæ of bone substance penetrated by communicating channels; within it the living cells are entrapped in lacunæ, and the lamellæ are bound by fine fibrils. This closely bonded structure is essential for strength. For the more active, vital and cellular process of repair this must be changed. This change is called resorption.

Resorption is preceded by vascular dilatation and decalcification, and there is a loss of organic material as well; the process is not a simple leaching out of calcium. This resorption opens the weave and converts the fine-fibrilled, lamellated bone into coarsely woven, unlamellated, primitive bone, which can then proceed to repair. These changes demand a good blood supply.

Blood Supply.

When the periosteum is stripped off the bone surface, this surface is dependent on collateral vessels to keep it supplied with blood. These are usually inadequate and there occurs some sequestration. Sequestration will also occur at the cortical ends of a fracture of long bones, when there is extensive destruction of blood vessels. Similarly, fragments and sections of bone will sequestrate to varying degrees.

Creeping Substitution.

Secondary revascularization can occur, provided that there is an adequate background of blood supply to encourage the growth of new blood vessels into these ghosts of living bone. The new advancing stream of life will replace the dead cells and begin the process of revitalization. This replacement is slow. Eighteen months to two years are necessary if the fragment is large.

There are other important details of this process which are essential to our understanding of fracture healing.

Blood Clot and Organization.

Blood is trapped between the bone ends by the periosteal sleeve. This may be torn, and then the surrounding tissues hold it. The blood organizes and develops into primitive granulation, in which there occurs early development of bone, provided there is good blood supply.

Much slower is the formation of bone from cartilage which will form in the clot at points where the oxygen tension is below a critical level.

Fibrocartilage Formation.

We know how movement and permanent restriction of blood supply at the bone ends will form fibrocartilage, resulting finally in pseudo-arthrosis and non-union.

Surgery must aid this process. The surgeon must appreciate these vital phases.

Damage to Blood Vessels.

Unskilful manipulation can further reduce the blood supply to the fracture area. This is more likely to happen when the manipulator is being guided by the X-ray film and exerts excess force in an attempt to obtain an anatomical reduction. This is more likely if the displacement is a few days or weeks old and soft tissue damage has occurred.

Strangulation of the periosteal sleeve will follow excess traction, which appears to be an important cause of delayed union. This complication is less frequent when traction is used to maintain rather than to obtain reduction.

Operative reduction must always increase the local trauma. Some forms of internal fixation do this more than others. I shall try to show you that intramedullary fixation requires less disturbance at the fracture site than other forms of fixation — for example, the application of a plate. If the pin is inserted blindly then the local circulatory disturbance from the fracture itself may not be increased.

Chemical Changes.

The metabolic changes immediately after and surrounding a fracture result in an acid medium in the early stages. This changes with healing, and an alkaline tide appears about three weeks later. Open reduction performed late may reverse this and spell further delay. This should be considered when one is deciding to open the fracture.

Stability.

Stability is a relative term. A fracture is labelled unstable if it will not remain anatomically reduced. If we accept a position that is not strictly anatomical, but is functional and stable, union will usually occur. To hold such a fracture by a pin or a plate is not enough; mechanical rigidity should come from the cortical bone that is left. Even a massive steel Küntscher nail is not strong enough to hold alone. Pins and plates in intertrochanteric fractures will break or separate at the angle if there is comminution of the cortex, and this is held open in the position of coxa valga. This principle applies when the dorsal cortex of a Colles's fracture is comminuted. The formation of living adult bone from a cortical graft takes many months of creeping substitution. It takes even longer to form from blood clot.

A Modern Method of Internal Fixation.

There are many methods that are available for the internal fixation of long bones, most of which use metal devices in one form or another. Before we consider some of these let us list a few principles.

1. Any method of fracture fixation must not disturb healing.

2. There must be sound mechanical fixation, with or without additional external methods.

3. The materials used must be completely inert, or if not completely inert, easily removable.

4. The technique should not be too difficult for a well-trained surgeon and his team.

5. The ability to allow early mobilization of the patient, in bed or out of bed, while healing is taking place is a great advantage.

Let us consider the first principle. Blind intramedullary pinning should have the least effect on the blood supply. If this does not succeed, then reduction through a small incision and fixation with an intramedullary pin would also do little damage. There would be further stripping of soft tissues if the retrograde method were used, because one or both the fragments would have to be exteriorized. Fixation with one or more screws can often be done with very little disturbance. It is generally accepted that plating and the presence of excess metal

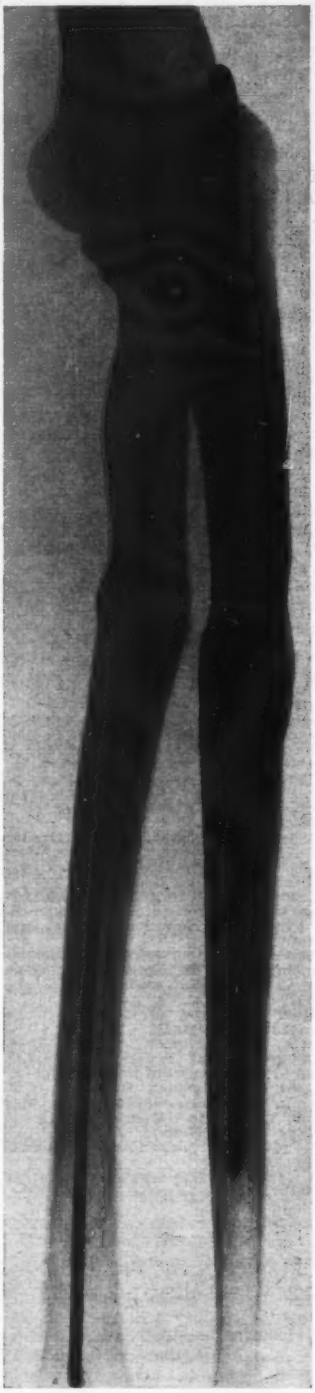


FIGURE I.

tends to delay union. Eggers developed a slotted plate, because he believed that the compression of contracting muscles would cause impaction and reduce this factor. There seems little doubt that a small gap (Ellis, 1958)

ILLUSTRATION TO THE ARTICLE BY W. W. WOODWARD.

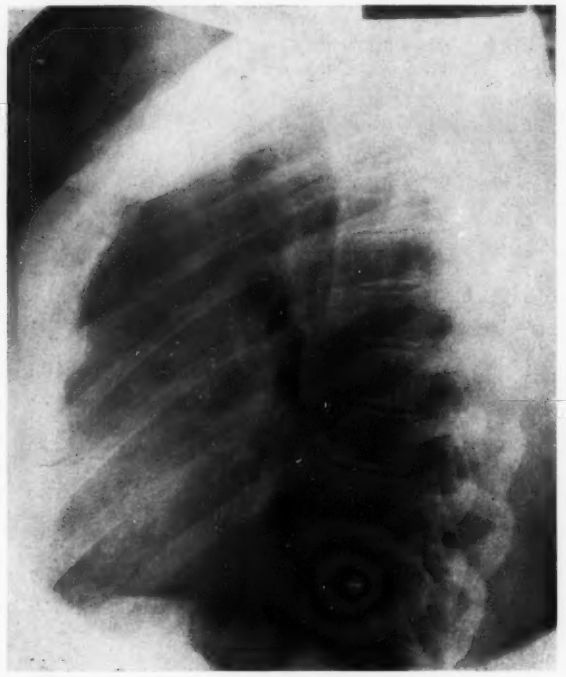


FIGURE I.

ILLUSTRATIONS TO THE ARTICLE BY T. S. REEVE.

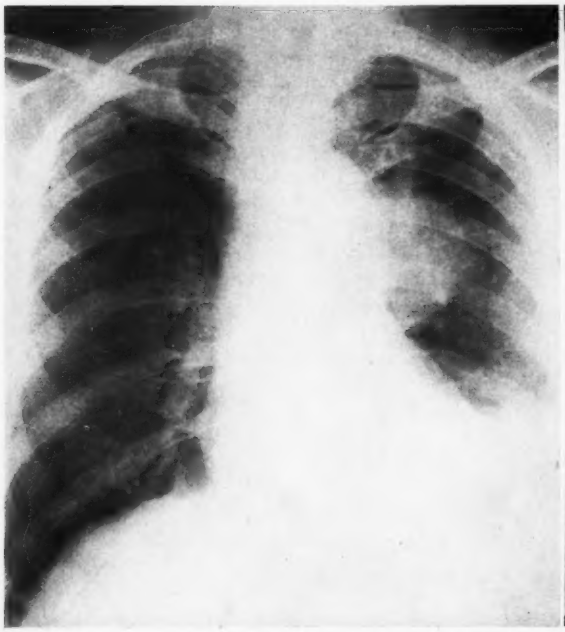


FIGURE II.

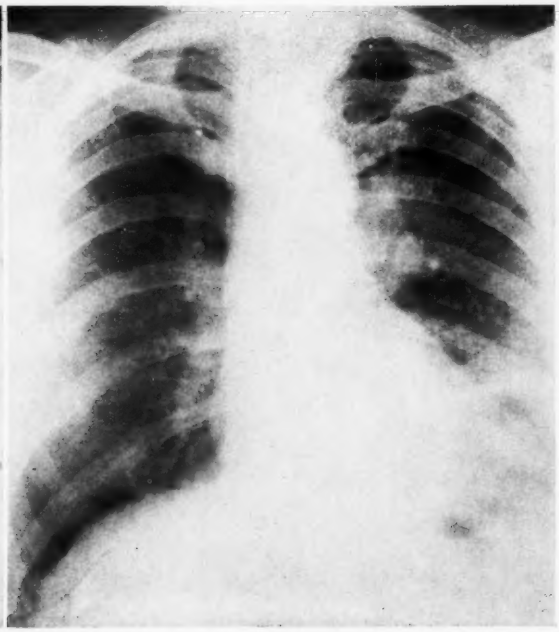


FIGURE III.

ILLUSTRATIONS TO THE ARTICLE BY P. E. HURST AND M. N. I. WALTERS.

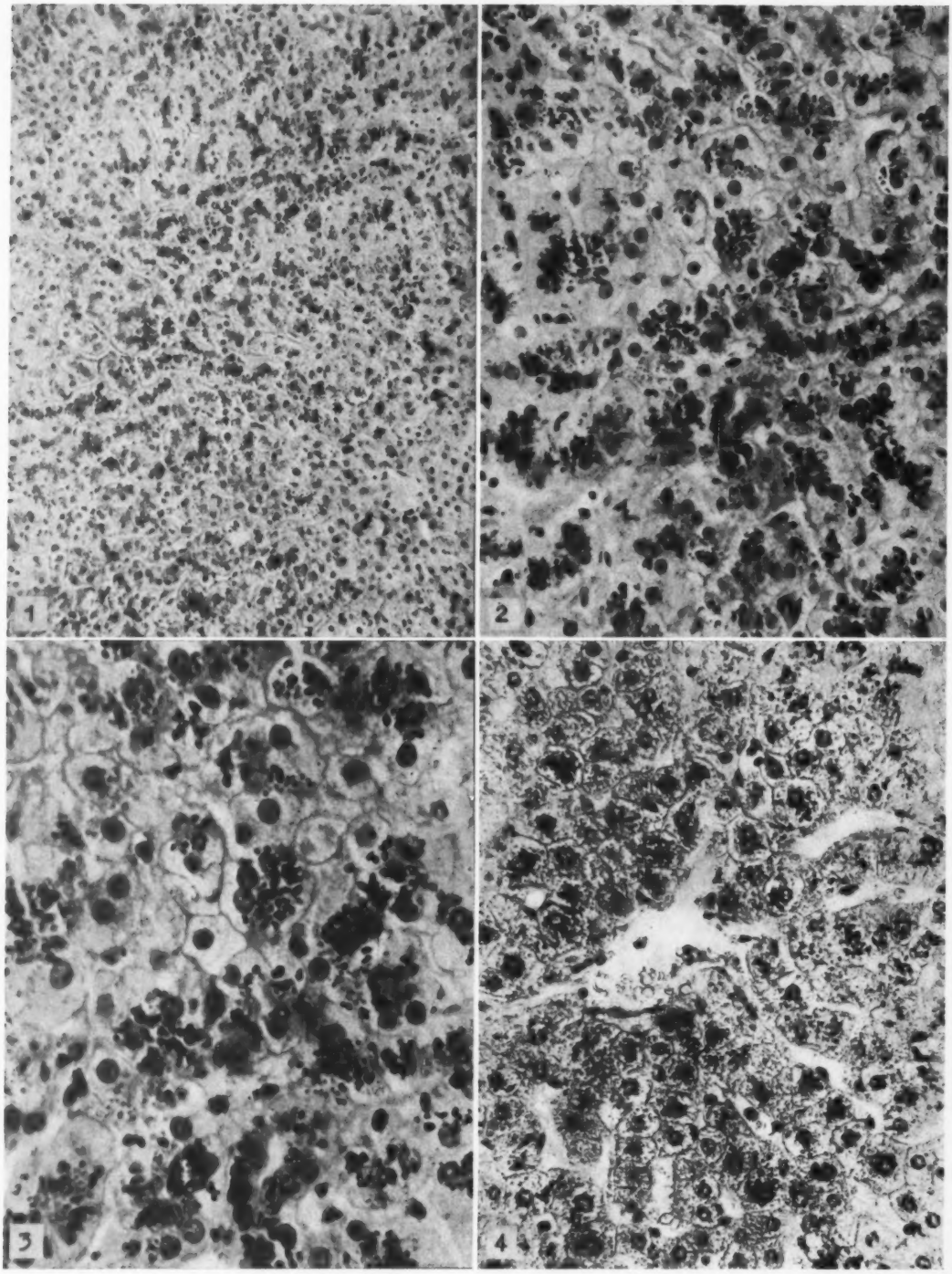
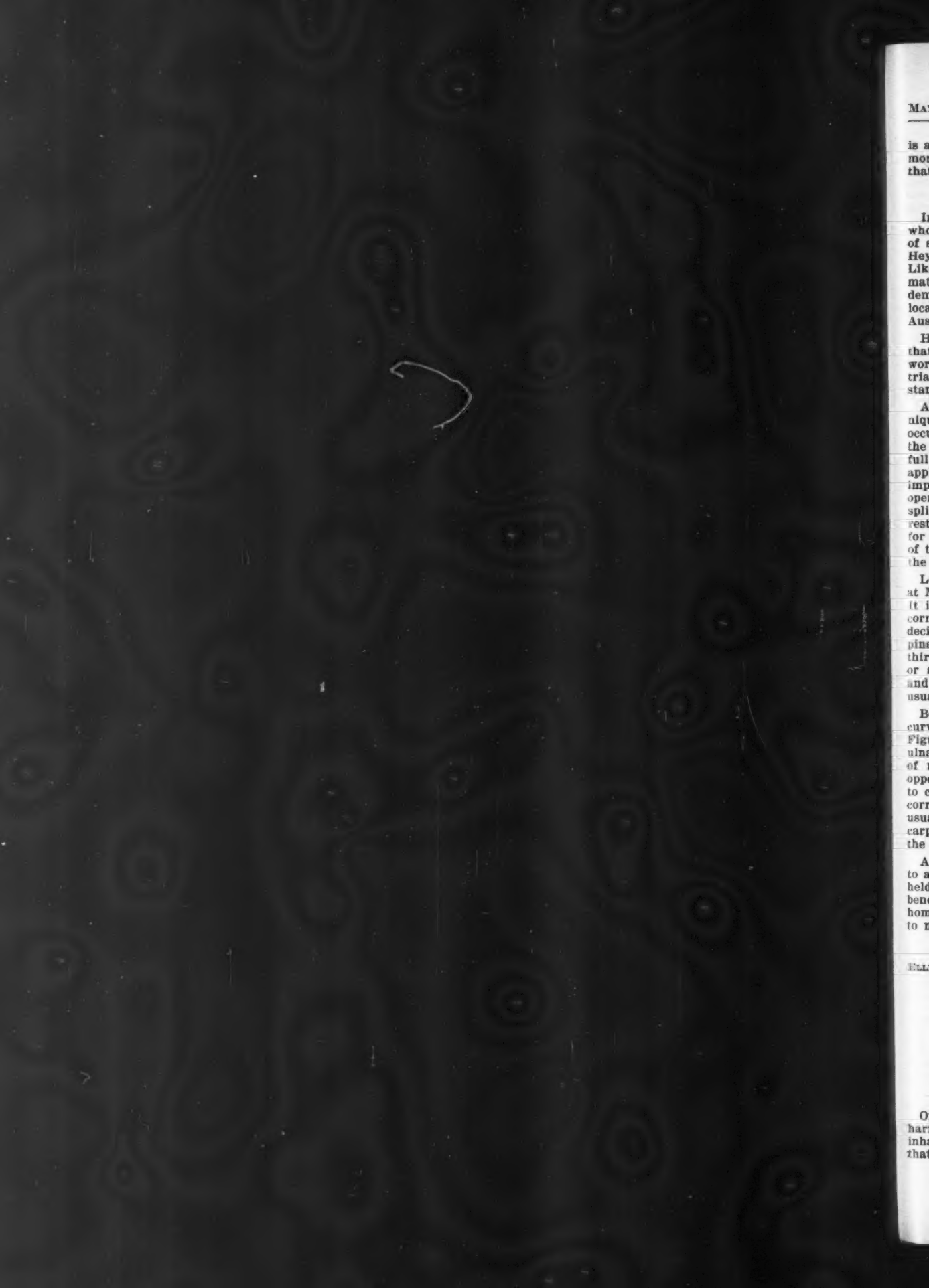


FIGURE I.—Case I: Liver biopsy. (Hæmatoxylin and eosin stain, × 41.) FIGURE II.—Case I: Liver biopsy showing hepatocellular pigment. (Hæmatoxylin and eosin stain, × 100.) FIGURE III.—Case I: Liver biopsy showing hepatocellular pigment. (Hæmatoxylin and eosin stain, × 520.) FIGURE IV.— Case II: Liver biopsy showing centrilobular distribution of pigment. (Hæmatoxylin and eosin stain, × 100.)



is an important cause of delay. However, plating requires more exposure and soft tissue damage than the methods that have been mentioned.

Intramedullary Fixation.

Intramedullary fixation is not a new method. Küntscher, whose name is often coupled with the technique, was one of several who applied the method during World War II. Hey Groves used massive nails in England about 1910. Like Lane, he was defeated by the need for non-corroding materials. This problem can be controlled now, but still demands care and a constant check on the sources of locally manufactured materials by the surgeon in Australia.

Here in Australia we are faced with certain difficulties that are less important in England and America. The worst of these is penny-pinching, which prevents expensive trials. Methods usually have to be reasonably proved and standardized.

Any lengthy treatise on Küntscher intramedullary techniques lists many dangerous complications which can occur. To avoid these, good equipment, particularly for the extraction of the nails, is a vital need. Nails in a full range of sizes and lengths must be available, and this applies also to reamers. Reamers are all the more important if the surgeon aims at a tight fit, so that post-operative mobilization can be complete and all external splinting can be avoided. Even the Küntscher method is restricted, and clover-leaf shaped, rigid nails are advocated for the mid-shaft of the femur and perhaps for the shaft of the humerus; smaller, V-shaped nails are advocated for the ulna.

Leslie Rush developed an intramedullary pin in 1927 at Meridian, Mississippi, in the United States of America. It is made of 18/8 "S.Mo." stainless steel, which is non-corrosive and, more important still, in its general use decidedly malleable. There are four sizes only of these pins: one-quarter, three-sixteenths, one-eighth and three-thirty-seconds of an inch respectively. The point is sledge or sloping in shape, and blunt. The head has a curve and a sharp tip. The pin is round and comes in the usual lengths.

Because it is malleable the pin can be inserted down curved bones or down straight bones from the side. Figure I shows one inserted in a radius and one in an ulna. In this operation the bone is broached at an angle of no more than 40 degrees and the pin skids off the opposite cortex and beds itself into the medullary canal, to curve against the near cortex. If the length is judged correctly this will give fixation at three points, which is usually firm. A pin inserted in this way will hold metacarpals and malleoli as well as comminuted shafts of the femur.

A certain amount of judgement and skill is necessary to adjust the final pressures so that smaller fragments are held correctly in position. This is usually achieved by bending the proximal end of the pin before it is driven home. It is important to judge the correct length of pin to make this correct.

Reference.

ELLIS, H. (1958), "The Speed of Healing After Fracture of the Tibial Shaft", *J. Bone Jt Surg.*, 1: 42.

ON OXYGEN POISONING UNDER WATER.

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OXYGEN TOXICITY is a term applied to the observed harmful effects which may be associated with the inhalation of oxygen at a partial pressure in excess of that encountered in atmospheric air. Under standardized conditions, the response varies widely between individuals and also from time to time in the one subject.

By far the greatest risk is involved in skin diving when oxygen rebreathing equipment is used. In a serious incident of "oxygen poisoning", such as may occur under water, there is often little or no useful warning (Donald, 1947).

For practical purposes, the history dates back to 1847, when Paul Bert demonstrated the condition during studies of animal life in oxygen-filled pressure chambers. It became somewhat of a scientific curiosity and attracted considerable attention, as evidenced by the exhaustive reviews of Stadie, Riggs and Haugaard (1944), of Bean (1945), of Ohlsson (1947) and, more recently, of Scano (1958).

From the viewpoint of underwater medicine, World War II saw the realization of the concept of free-swimming naval clearance divers equipped with self-contained oxygen rebreathers. This abruptly focused attention on the hazards of oxygen toxicity. A term "shallow-water blackout" came into use to cover unpleasant incidents which are now divided into several categories — hypoxia, carbon dioxide toxicity, hyperventilation and "oxygen poisonings".

The most elaborate studies on shallow-water blackout were carried out by Donald (1947) under wartime conditions at the Siebe Gorman establishment. Two thousand subjects were used. The effects during the breathing of pure oxygen at 3·6 atmospheres absolute (pressure of oxygen = 2700 mm. of mercury) were strikingly similar to those of anoxia, progressing to coma and convulsions. The whole cerebro-spinal axis was involved. Tolerance was inexplicably less while under water, and decreased further with exercise.

Comroe *et alii* (1945) recognized a syndrome of respiratory symptoms in their subjects who breathed 100% oxygen at ground level for 24 hours. Substernal distress came on after an average of 14 hours, and there were also symptoms and signs of rhinitis, pharyngitis, Eustachian block, and diminished vital capacity. This syndrome was considered to represent local toxic changes as the counterpart of severe pulmonary lesions in animals.

As yet, there is no workable concept to account for the occurrence and vagaries of oxygen poisoning under water in man. In any other circumstances, the simple term "anoxia" would be applied to the syndrome consisting of raised tissue lactic acid level at rest, in the presence of essentially normal venous blood values for hæmoglobin, carbon dioxide pressure and pH, with all the signs and symptoms of anoxia.

When reference is made to oxygen toxicity, an illusory distinction is drawn between the pulmonary lesions which probably cause the death of experimental animals, and the neurological phenomena preceding shallow-water blackout in man. However, Grognot and Chomé (1954) prevented the pulmonary lesions from appearing in hyperoxic guinea-pigs with chlorpromazine prophylaxis. Tetraethylammonium bromide was of benefit also, but to a lesser extent. This evidence refuted the local toxicity concept of Comroe *et alii* (1945) under these experimental conditions. Bean (1956) also reported protection with chlorpromazine against the development of pulmonary lesions in rats exposed to oxygen at 6·8 atmospheres absolute. In a later study, Bean and Wagemaker (1960) showed that the probable action of chlorpromazine in such cases was through suppression of hypothalamic responses.

Malette and Eiseman (1958) reported another paradox. These workers hyperventilated dogs with 100% oxygen at ground level and then performed analyses on blood and cerebral tissue. Although arterial oxygen concentrations had risen, lactic acid estimations revealed rises of 13·5% in the jugular venous blood and a 67% increase in cerebral tissue lactic acid content, as compared with the controls ($P = 0{\cdot}001$). It was considered that the cerebral anoxia demonstrated was the result of the Bohr

effect of decreased oxyhæmoglobin dissociation, and also some cerebral vasoconstriction.

A third significant recent study was that of Sugioka and Davis (1960), who reported on experiments involving the implantation of oxygen electrodes in the cerebral cortex of the dog. With these sensitive detectors, depressed cerebral oxygen tensions were demonstrated during hyperventilation with air and also 100% oxygen. Marked increases were noted in the cerebral oxygen tension when 10% carbon dioxide was added to the air during hyperventilation, and a further increase if 10% carbon dioxide in oxygen was employed.

In applying these findings to man with a minor shift of the emphasis, it is evident that if hyperventilation accompanies exposure to high concentrations of oxygen, then a paradoxical cerebral hypoxia will result, with development of the phenomenon described as oxygen poisoning. The onset and progress of the symptoms is thus capable of wide variation, the most likely causes of hyperventilation being use of breathing apparatus, excitement, inexperience, the growing threat of oxygen poisoning and also poor visibility under water (Burke, 1960).

Preoccupation with the synergism of carbon dioxide accumulation and oxygen toxicity, as described in United States Navy data (1956) and by Scano (1958), has prevented hypocapnia from receiving due attention. Lambertson and his group (1953) had already demonstrated cerebral vasoconstruction and hyperventilation on subjects breathing oxygen from a demand system at 3·5 atmospheres absolute. The observed decrease in arterial carbon dioxide pressure and the slight increase of 3 mm. of mercury in jugular venous carbon dioxide pressure were studied further. Significant ($P = 0{\cdot}01$) increases were found in tidal and respiratory minute volumes, and decrease in the carbon dioxide pressure of alveolar air.

However, it must also be accepted that oxygen has its own peculiar toxic effect, as evidenced in the study of Comroe *et alii* (1945). The 10 air-breathing controls showed less severe respiratory tract reactions without substernal discomfort. The argument loses some force because, although none of Comroe's six subjects at 18,000 feet for 24 hours (oxygen pressure 380 mm. of mercury) experienced substernal discomfort, all seven personnel studied by Michel *et alii* (1960) developed this symptom on their second day at an oxygen pressure of 418 mm. of mercury. Perhaps if the above-mentioned controls had continued their air breathing a little longer, the typical oxygen toxicity pattern would have been clearly demonstrated.

Concept.

The problem of oxygen poisoning under water appears to be capable of solution, at least in part. A concept is presented that the incidents are the result of hyperventilation combined with and also inducing cerebral hypoxia, the hyperventilation being initially provoked by an autonomic reflex activated by oxygen breathing. From this concept the following deductions can be drawn.

1. A variability in individual response stems from a summation of factors involving personality profile, experience, excitement, malaise, menses, and tolerance to hypocapnia, hyperoxia and alcohol.

2. A variability in under water response depends on the combined influence of the foregoing factors on the conditions encountered: depth, duration of exposure and degree of hypocapnia, with allowances for performance of the carbon dioxide absorber. The water temperature is involved if causing discomfort (Donald, 1947), and visibility is important to some subjects.

3. The futility of setting safe exposure levels in oxygen diving becomes apparent; at the same time, it would appear that the individual may, with care, extend his personal tolerance.

4. There are two alternative adverse influences of under water exercise. Hyperventilation exceeding the actual respiratory requirements may accompany the commencement of exercise and its continuance. Sensations of extreme fatigue are induced by hypocapnia and cerebral hypoxia, with exaggeration of hyperventilation similar to failure of development of the "second wind" in track runners. Alternatively if the absorber is unable to cope with the load, strenuous exercise may lead to a toxic build-up of carbon dioxide pressure. Also, other autonomic factors may be implicated in exercise.

5. Because of synergisms between hyperventilation, hypoglycæmia, hypoxia (Brown, 1953) and malaise, any skin diving, especially oxygen diving, is contraindicated with malaise.

Summary.

1. In man, the inhalation of 100% oxygen at ground level leads to the slow appearance of respiratory symptoms resembling progressive coryza.

2. In skin diving during the breathing of oxygen, neurological effects predominate and the reaction is accelerated.

3. A concept is presented to implicate hyperventilation in "oxygen poisoning", with resultant symptoms of cerebral hypoxia.

4. So many variables are involved that it is futile to speak of safe depth-exposure times during the use of oxygen-rebreathing equipment.

References.

BEAN, J. W. (1945), "Effect of Oxygen at Increased Pressures", *Physiol. Rev.*, 25: 1.

BEAN, J. W. (1956), "Reserpine, Chlorpromazine and the Hypothalamus in Reactions to Oxygen at High Pressure", *Amer. J. Physiol.*, 187: 389.

BEAN, J. W., and WAGEMAKER, H. (1960), "Brain Blood Flow, Chlorpromazine (Thorazine) and its Protective Action Against the Toxicity of Oxygen at High Pressure", *Amer. J. Physiol.*, 198: 341.

BROWN, E. B. (1953), "Physiological Effects of Hyperventilation", *Physiol. Rev.*, 33: 445.

BUREAU OF MEDICINE AND SURGERY (1956), "Submarine Medicine Practice", NAVMED-P5054, U.S. Government Printing Office, Washington.

BURKE, D. T. (1960), "Vision Underwater", read at the 17th annual meeting of the Ophthalmological Association of Australia (B.M.A.).

COMROE, J. H., JR. AIPPS, R. D., DUMKE, P. R., and DEMING, M. (1945), "Oxygen Toxicity", *J. Amer. med. Ass.*, 128: 710.

DONALD, K. W. (1947), "Oxygen Poisoning in Man", *Brit. med. J.*, 1: 667, 712.

GROGNOT, P., and CHOMÉ, J. (1954), *"Action de la chlorpromazine et du tétrylammonium sur les réactions pulmonaires provoquées par inhalation d'oxygène pur"*, *C.R. Soc. Biol.*, 148: 1474.

LAMBERTSEN, C. J., KOUGH, R. H., COOPER, D. Y., EMMEL, G. L., LOESCHCKE, H. H., and SCHMIDT, C. F. (1953), "Oxygen Toxicity. Effects in Man of Oxygen Inhalation at 1 and 3·5 Atmospheres upon Blood Gas Transport, Cerebral Circulation and Cerebral Metabolism", *J. appl. Physiol.*, 5: 471.

LAMBERTSEN, C. J., STROUD, M. W., GOULD, R. A., KOUGH, R. H., EWING, J. H., and SCHMIDT, C. F. (1953), "Oxygen Toxicity. Respiratory Responses of Normal Men to Inhalation of 6 and 100 Per Cent Oxygen under 3·5 Atmospheres Pressure", *J. appl. Physiol.*, 5: 487.

MALETTE, W. G., and EISEMANN, B. (1959), "Cerebral Anoxia Resulting from Hyperventilation: A Dangerous Paradox", *Aerospace Med.*, 29: 611.

MICHEL, E. L., LANGEVIN, R. W., and GELL, C. F. (1960), "Effect of Continuous Human Exposure to Oxygen Tension of 418 mm. Hg. for 168 Hours", *Aerospace Med.*, 31: 138.

OHLSSON, W. (1947), "Study on Oxygen Toxicity at Atmospheric Pressure", *Acta med. Scand.*, 128: 1, Suppl. 190.

SCANO, A. (1958), *"L'iperossia"*, *Riv. Med. Aeronaut.*, 21: 88, 337, 539, 765.

STADIE, W. C., RIGGS, B. C., and HAUGAARD, N. (1944), "Oxygen Poisoning", *Amer. J. med. Sci.*, 107: 84.

SUGIOKA, K., and DAVIS, D. A. (1960), "Hyperventilation with Oxygen: A Possible Cause of Cerebral Hypoxia", *Anesthesiology*, 21: 135.

EXTERIOR GESTATION AND LIFE SET.

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A PREVIOUS PAPER (Bostock, 1958) outlined a concept of exterior gestation — that intrauterine life is terminated, not because the fœtus is adequately matured for departure from the uterus, but because it faces catastrophe if its emergence is delayed. An enlarging head must pass through a fixed pelvic outlet. One must therefore regard gestation as occurring in two stages — the first within the womb, and the second upon the breast. There is an interior and exterior gestation which approximate in duration. The fœtus is an "intragestate", and an infant during the first nine or 10 months of life is an "exterogestate", as suggested by Dr. Ashley Montague (1959).

Trauma, in the nature of overstimulation or rejection, can, in the exterogestate, produce effects which continue into childhood. They include disturbance of sleep, enuresis and asthma. The purpose of this paper is to record the fact that accompanying personality changes can be sufficiently long-lasting to warrant the use of the term "life set".

Details of Personality Change.

Details of the personality changes in enuretic children were derived from an investigation of a series of 50 children aged between six and 12 years suffering from essential enuresis. In each case an organic factor was excluded. The patients were consecutive and satisfied the criteria of having no fewer than three bedwetting nights per week, of not being mental defectives and of having reasonably cooperative parents. Each child was seen on several occasions.

The children tended to exhibit social maladjustment, as shown by their impaired ability to mix freely with friends or siblings, and by school performance below the level anticipated from their intelligence quotient.

Fear of the dark was almost universal and was reflected in the number who sought their mothers' beds at night. Many children shut their windows even in hot weather, while others covered their heads with bedclothes to escape danger.

Projection testing with Murray's Thematic Apperception ("make a picture story"), puppet play and blackboard drawing confirmed the existence of undue fear, both in the dark and in the day. It was characteristically linked with the fear of physical injury of a mutilating type. The children were immune to the fear of theft, of being vaguely chased or of being kidnapped, but had a dread of mutilation. Many lay passively in bed, dreaming they were shot, cut up or dismembered.

Summarizing our findings, we found that the enuretic profile reveals a reluctance to assume responsibility, and the night fears show an unresolved reaction to a situation which has no existence in reality.

The results give a factual background for an impression, based on observation of much clinical material, that essential enuresis is associated with abnormalities of a specific type in the personality pattern.

The next step is consideration of their degree and permanence.

The Depth of the Personality Abnormality.

The depth of the personality abnormality can be gauged from critical examination of children who have received intensive therapy, and from the results of this therapy.

The group of 50 cases mentioned above provided material for this study. As is usual in the case of enuretics, not all the patients persisted in treatment; in 27 cases only was our information considered to be adequate. Each of these was followed up for at least 18 months.

From Table I the results of the treatment given can be seen.

TABLE I.
Results of Treatment of Enuretic Children.

	Group I.		Group II.	Total.
	Improvement Followed by Relapse.	No Improvement.	Improvement Without Relapse.	
Male patients ..	6	4	8	18
Female patients ..	2	1	6	9
Total ..	8	5	14	27

The boys and girls who relapsed or who did not improve presented excessive dependent traits; they were fearful, inhibited and passive. Their behaviour was patterned on what they conceived to be their mothers' wishes. At the same time, great hostility was revealed, but this had to be repressed at all cost; perhaps its expression was possible only in sleep, as enuresis. They did not mix freely with other children; social adjustment was noticeably poor, and despite their high intelligence levels their school work was substandard. The essential feature of this therapeutically unsatisfactory group of children is that their personalities were inadequate to face stresses which should be surmountable within their age range. They sought to retain the dependency on their mothers, as in babyhood.

Both boys and girls who did not relapse had personalities more tinged with aggression; they dealt with their problems by refutation and assurance. Ambition was evident, as was the ability to cope with situations within the ambit of their age range. School reports were good.

The essential feature of this therapeutically satisfactory group of children is that they exhibited a greater degree of behavioural adequacy and less maternal dependency than the therapeutically unsatisfactory group.

Can the Personality Deviations be Permanent?

The cases recorded in the last section were in the age range of seven to 12 years. Our next objective is to ascertain if adult enuretics retain their dependent attitudes.

Pierce *et alii* (1956) have written a lucid account of psychiatric interview studies of 60 enuretic naval recruits as contrasted with those of 60 non-enuretics. The controls were carefully matched. The clinical interviews were made by the same medical officer and vital information was obtained from official reports. To complete the history, social service reports were obtained from the home town of each enuretic. The enuretic group revealed a "wide variety of phobic reactions". It was noted that 18 of the enuretics and only three of the controls had nyctophobia.

With regard to the over-all personality pattern, the authors state: "Dependency conflicts loom ubiquitously and detrimentally penetrate all facets of their lives." In dealing with the inability of these people to cope with the adult problem of sex, they remark that "such striving is doomed to failure because they are unable to relinquish their fantasy of themselves as helpless little boys, or to banish their conscious image of their own inadequacy. Each realistic failure in life, whether it be in school, or in the gang, or in the service, further entrenches their need to gratify dependency and further

confirms their belief in their own inferiority". They regard them as the possessors of a "Peter Pan complex".

Benowitz (1946), in a study of 172 enuretics, confirms the findings of Pierce *et alii*. No less than 50% of his patients married in order to find a second mother, by whom to be loved as in infancy.

A comparison of the groups of child and adult enuretics show two features in common — a tendency to fear of the dark and an inability to reach emotional maturity.

Validity Tested by Rejection of the Exterogestate.

The validity of the hypothesis that interference with exterior gestation creates a life set can be tested in another way. Rejection in the place of overstimulation might be expected to produce another type of personality setting. The experiment has been made.

Among our case histories were 29 non-enuretic children who had been bottled-fed from the age of two months or less. Although the bottle may be socially acceptable, many believe it creates a feeling of rejection in the infant. The neogestate is deprived of the warm security of the breast and a mode of feeding which is instinctive.

Close examination of the mothers of the 29 children disclosed that in no case had they enjoyed an adequate mother-child relationship in their own childhood. They came to child-bearing as a chore to be feared or a burden to be shouldered. The maternal outlook undoubtedly reinforced the bottle-feeding situation in creating a climate of rejection.

The 29 children were seen on several occasions, and projection tests, including Murray's Thematic Apperception Test and play interviews, were given to each child. The children revealed an insatiable desire for proofs of affection, gifts and praise. They were anxious, felt insecure and were unable to form close personal relationships. Sibling rivalry tended to be intense and was carried over to other children. There was over-compensation, which resulted in truculent demands and domineering attitudes. Compulsive tendencies forced some of them to be perfectionists and sticklers for detail. Their chief fear hinged on their mothers' disapproval or desertion.

The hallmark of the children's emotional state was basic insecurity. It differed materially from that of children who, as exterogestates, were exposed to motherly overstimulation. Thus it would appear that overstimulation and rejection of the exterogestate are associated with differences in personality pattern.

The permanence of the life set in the case of the rejected children awaits confirmation but there are straws in the wind. Our researches implicate asthma as one of the side effects of rejection. Recently we have concluded a research on adult asthmatics (Bostock, 1960). There is considerable evidence that the basic insecurity observed in the child asthmatic is present in the adult.

Summary.

The authors restate the concept of exterior gestation. It is a period of eight to ten months after birth to be regarded as an extension of intrauterine gestation, and should be treated as such. Failure to do so has tangible repercussions.

Series of cases are cited in which (i) overstimulation and "over-mothering" of the exterogestate creates a specific personality pattern (evidence is given to show that this may last into adulthood); (ii) bringing up the exterogestate in a climate of rejection produces insecurity and anxiety (this also may last into adulthood).

It is concluded that interference in the exterior gestation period can determine the pattern for an individual's "life set".

Acknowledgements.

Our sincere thanks are due to the late Professor Alexander Kennedy, and to Dr. P. C. Fawcett, of Edinburgh, for much helpful criticism and assistance; to Dr. Aubrey Pye, Medical Superintendent of the Brisbane General Hospital, and to Dr. D. C. Fison, Medical Superintendent of the Brisbane Children's Hospital, for access to clinical material and valuable suggestions; and to the Commonwealth of Australia and the University of Queensland for grants which made the research possible.

References.

BENOWITZ, H. H. (1946), "The Enuretic Soldier in an A.A.F. Basic Training Centre", *J. nerv. ment. Dis.*, 104: 66.

BOSTOCK, J. (1960), "Does Asthma Originate After Infancy?" MED. J. AUST., 2: 858.

BOSTOCK, J. (1958), "Exterior Gestation, Primitive Sleep, Enuresis and Asthma: A Study in Ætiology", MED. J. AUST., 2: 149.

MONTAGUE, M. F. A. (1959), personal communication.

PIERCE, C. M., LIPCON, H. H., MCLARY, J. H., and NOBLE, H. F. (1956), "Enuresis Psychiatric Interview Studies", *U.S. armed Forces med. J.*, 7: 1265.

Reports of Cases.

POSTERIOR MEDIASTINAL GOITRE: EFFECT OF FLUOROSCOPY ON CHOOSING SITE FOR INCISION.

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GOITRES in the posterior mediastinum seem to be less rare than was thought 10 years ago. Keynes (1950) described two then, and noted that Joll, despite his immense documentation of thyroid abnormalities, had described none. Morris (1955) described 11 examples, and the bibliographies given by Tomkinson (1951), Morrison (1958) and the authors listed at the end refer to a further 59 such goitres, though it must be admitted that these varied greatly in their downward extent.

The present report aims, first, to recall goitre to mind in the pre-operative diagnosis of posterior mediastinal opacities, and second, to reemphasize the value of demonstrating by fluoroscopy that the opacity moves when the patient swallows. This can alter the operative approach from a diagnostic thoracotomy to an ordinary Kocher's collar incision. The cervical approach has the advantage of allowing early control of the inferior thyroid artery, usually the principal artery to a goitre in the upper mediastinum.

Clinical Record.

Mrs. A., aged 34 years, was referred to the writer in August, 1958, by Mr. R. Ferris. She had no symptom. Mass radiography of the chest had disclosed an opacity on the right side. A lateral film showed this to be a large sausage-shaped opacity and to be in the posterior mediastinum (Figures I[1] and II). Fluoroscopic screening by Dr. R. E. Grant showed that the opacity moved on swallowing. As no abnormality was found at œsophagoscopy, this demonstration gave the pre-operative diagnosis of posterior mediastinal goitre.

On August 20, 1958, at St. Luke's Hospital, Launceston, under general anæsthesia by Dr. K. S. Goulston, the goitre was removed through a Kocher's collar incision. A bridge of thyroid tissue passed directly backwards from the right lower pole to join the mediastinal mass. The diameter of the right inferior thyroid artery was enlarged to about three times the usual size. It was ligated, and a finger was then passed down into the mediastinum with the object of feeling for vessels. Occasionally the arterial supply is not through the inferior thyroid, or not through it alone, but comes from large mediastinal vessels, even from the aorta (d'Abreu, 1953). Moreover, some of these goitres have veins draining directly into the innominate veins, the

[1] For Figure I see art-paper supplement.

venæ cavæ or even the right atrium (Keynes, 1950). Had such vessels been encountered, it might have been necessary to add a thoracic exposure. However, no such vessels were felt, and so the mass was delivered into the neck. The mediastinal tissue differed in appearance from the cervical thyroid tissue, being browner and containing obviously fibrotic, even calcified areas; from a technical viewpoint it was of interest that its surface was far less vascular than the cervical thyroid tissue. An orthodox partial thyroidectomy was done, the whole specimen being shown in Figure III. A drain tube placed in the posterior mediastinum was brought out through the right end of the skin incision and removed after 24 hours. On microscopic examination, both the mediastinal and the cervical thyroid tissue had the appearance of inactive colloid goitre. The post-operative course was uneventful, and the patient has remained well.

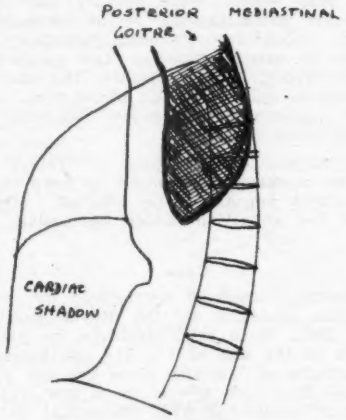

FIGURE II.

Discussion.

Pre-Operative Diagnosis.

The importance of pre-operative diagnosis is that it will lead in a suitable case to a cervical incision, and so to the early control of the inferior thyroid artery, usually the principal artery to a goitre in the mediastinum. On the other hand, should a diagnostic postero-lateral thoracotomy be done and the opacity turn out to be a goitre, it may be difficult from the chest to secure this vessel without endangering the recurrent laryngeal nerve. Indeed, with the use of postero-lateral thoracotomies, Ellis, Good and Seybold (1952) reported three recurrent nerve palsies in 11 cases.

As in reports by Morris (1955), by Hirschfeld (1951), by Wightman and Windsor (1951) and by other authors, the shadow reported here moved on swallowing. This was the crucial observation. Neurogenic tumours or enlarged lymph nodes, the more common occupants of the posterior mediastinum, do not move on swallowing; nor, of course, do aneurysms or bronchial cysts, lesions mentioned in the differential diagnosis by McMahon (1951).

Radioactive iodine has been used for diagnosis by Touroff (1950), but was not used in the case now reported because, with qualifications irrelevant here, the writer dislikes the use of radioactive substances. Hydatid disease is so common in the southern parts of Australia that one here would be wary about needling. Hence, even though the shape of the opacity was unlike a hydatid cyst, aspiration biopsy was also avoided.

Thoracic Approaches.

When the goitre is inaccessible from or too large for removal through the neck, three separate thoracic routes have been suggested. (i) Some authors have recommended splitting the sternum — for example, Keynes (1950) and d'Abreu (1953) — but Johnston and Twente (1956) illustrate the vascular obstacles confronting the operator who splits the sternum; the goitre lies behind the subclavian and innominate vessels and often behind the azygos vein and ascending aorta. (ii) Sweet (1949) made use of thoracotomy when a cervical incision proved inadequate. This requires movement of the patient during operation or a second operation. Thoracotomy as a second operation was required for the removal of the intrathoracic mass from a patient in Sydney (Rundle, 1960). (iii) Johnston and Twente suggest that when a combined cervico-thoracic approach is necessary, the thoracic incision should be made antero-lateral by incising the second intercostal space, ligating the internal

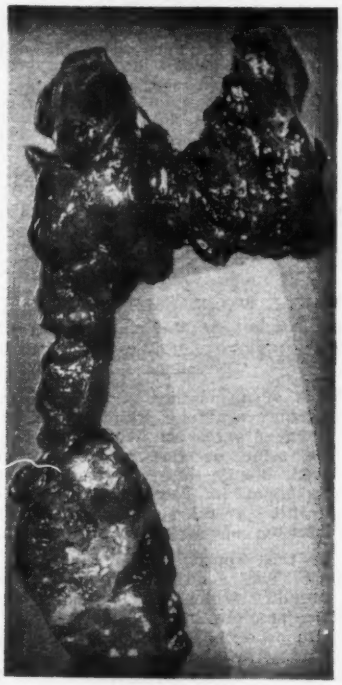

FIGURE III.

mammary vessels and dividing the second and third costal cartilages. This allows the patient to remain upon his back and gives access to the lower pole of the goitre, which can be pushed up into the neck. They state that axillary extension of their incision gives this access without transgressing the large vessels encountered in the transsternal approach.

Summary.

1. A cervical approach alone was sufficient for the removal from the posterior mediastinum of a goitre which had descended as far as the seventh rib.

2. The cervical approach allowed direct access to the vascular pedicle — that is, the inferior thyroid artery. To see this artery close at hand is an advantage. To reach for it from a thoracic exposure endangers the recurrent laryngeal nerve.

3. Of great value in pre-operative diagnosis was fluoroscopic demonstration of movement on swallowing.

4. A discussion is presented on the three routes proposed by other authors for opening the chest if a combined cervico-thoracic operation is necessary.

References.

D'ABREU, A. L. (1953), "A Practice of Thoracic Surgery", Arnold, London.

ELLIS, F. H., GOOD, C. A., and SEYBOLD, W. D. (1952), "Intrathoracic Goiter", *Ann. Surg.*, 135: 79.

HIRSCHFELD, K. (1951), "Tumours and Cysts of the Mediastinum. Part Two", *Aust. N.Z. J. Surg.*, 21: 81.

JOHNSTON, J. H., and TWENTE, G. E. (1956), "Surgical Approach to Intrathoracic (Mediastinal) Goiter", *Ann. Surg.*, 143: 572.

KEYNES, G. (1950), "Thyroid Surgery Fifty Years Ago, with a Contribution on Intrathoracic Goitre", *Brit. med. J.*, 1: 621.

MCMAHON, J. S. (1951), "Five Unusual Thoracic Cases", *Aust. N.Z. J. Surg.*, 21: 110.

MORRIS, K. N. (1955), "Posterior Mediastinal Goitre: A Report of 11 Cases", *Aust. N.Z J. Surg.*, 24: 241.

MORRISON, I. M. (1958), "Tumours and Cysts of the Mediastinum", *Thorax*, 13: 294.

RUNDLE, F. F. (1960), personal communication.

SWEET, R. H. (1949), "Intrathoracic Goiter Located in the Posterior Mediastinum", *Surg. Gynec. Obst.*, 89: 57.

TOMKINSON, J. S. (1951), "Posterior Mediastinal Goitre: A Report of Three Cases", *Brit. J. Surg.*, 38: 271.

TOUROFF, A. S. (1950), Discussion, *J. thorac. Surg.*, 19: 751.

WIGHTMAN, D. B., and WINDSOR, H. M. (1951), "Posterior Mediastinal Goitre", *Brit. J. Radiol.*, 24: 41.

BLACK LIVER JAUNDICE (DUBIN–SPRINZ SYNDROME).

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THE existence of an obscure group of diseases, often familial, producing recurrent jaundice over a period of years but without progressive hepatic damage, has been recognized for some decades. More frequent use of diagnostic liver biopsy and increased knowledge of bilirubin metabolism in recent years have permitted their division into several specific entities and allowed some comprehension of their pathological physiology.

The first of these entities was described by Gilbert *et alii* in 1907. This condition is characterized by the presence of jaundice which may be persistent or intermittent, being precipitated by intercurrent infection, emotional stress or excessive fatigue. The jaundice may be accompanied by mild malaise and anorexia, but not by abdominal pain. The serum bilirubin level is elevated, although rarely above 5 mg. per 100 ml., and the van den Bergh reaction is predominantly indirect. Bile does not appear in the urine. Oral cholecystography and liver biopsy usually reveal no abnormality. The condition is familial and apparently transmitted as a Mendelian dominant trait. Although described under a number of synonyms, including "familial non-hæmolytic jaundice" (Dameshek and Singer, 1941) and "constitutional hepatic dysfunction" (Comfort and Hoyne, 1944), the disease is usually known by the eponym "Gilbert's disease".

A similar disorder in infants was reported by Crigler and Najjar (1952). Marked elevation of the serum bilirubin level occurs shortly after birth and may be associated with kernicterus. The serum bilirubin may reach levels as high as 45 mg. per 100 ml., and is predominantly indirect reacting. This condition is probably the homozygous expression of the abnormality which produces Gilbert's disease in the heterozygous form. It is invariably fatal.

A second syndrome of familial non-hæmolytic jaundice has been recorded by Rotor *et alii* (1948) and by Haverback and Wirtschafter (1960). This condition resembles that described by Gilbert and his colleagues, but the serum contains both direct-reacting and indirect-reacting varieties of bilirubin, and bile appears in the urine. As in Gilbert's disease, liver biopsy and cholecystography reveal normal findings.

Another syndrome was independently reported in 1954 by two groups of workers, Dubin and Johnson and Sprinz and Nelson. Similar cases have since been described under a variety of names. Dubin (1958) has reviewed the 50 cases known to that time under the title of "chronic idiopathic jaundice", but as this would include all the familial hyperbilirubinæmias, a preferable name is "black liver jaundice", suggested by Bynum (1957). However, the most frequently used title is Dubin-Sprinz syndrome.

The disorder is characterized by an elevated serum bilirubin level of the direct-reacting type, by the presence of bile in the urine and by inability of the liver to excrete other substances into the bile. The symptoms include abdominal pain, nausea, vomiting, fatigue, dark urine and pale stools. Hepatomegaly may be present, and additional investigations reveal increased urinary urobilinogen excretion, "Bromsulphthalein" retention and failure of visualization of the gall-bladder with radio-opaque media. Macroscopically the liver is dark-grey or black in colour, and on histological examination the hepatic parenchymal cells are found to contain a dark golden-brown pigment.

It is the purpose of this paper to present a pedigree in which two members are known to have this disorder and two others appear to be affected. (Only details relevant to the condition under discussion have been reported.)

Case I.

A male patient, aged 56 years, and by occupation a vigneron, was admitted to the Royal Perth Hospital in August, 1953. Born in Yugoslavia, he had migrated to Australia at the age of 33. He had been subject to recurrent attacks of jaundice since the age of 12 years, when he had first been icteric for a few weeks. Thereafter jaundice associated with abdominal pain and the passing of dark urine had been recurring at intervals of three to 12 months, usually lasting a month.

On the patient's admission to hospital, slight icterus was present, together with pyrexia and signs of bronchitis and emphysema. The liver was palpable 3 cm. below the right costal margin. The serum bilirubin level was 2·6 mg. per 100 ml., and the result of Fouchet's test for bile in the urine was positive. Urinary urobilinogen excretion was increased, but the results of other tests of liver function appeared normal (see Table I). Hæmatological investigations, including hæmoglobin estimation, leucocyte and reticulocyte counts and the erythrocyte fragility test, gave normal results. A liver biopsy was performed, and this showed the appearance of Dubin-Sprinz syndrome (*vide infra*).

After his discharge from hospital the patient suffered recurrent attacks of bronchitis, and two years later, in 1955, he was readmitted to hospital. Jaundice and hepatomegaly were again obvious, the serum bilirubin level being 4·5 mg. per 100 ml. During a third admission in April, 1956, after a hæmatemesis from a chronic duodenal ulcer, the serum bilirubin level was 3·6 mg. per 100 ml.

Since this episode he has remained well, although his daughter believes jaundice to be noticeable at times. Oral cholecystography in 1957 revealed only a faint shadow of the gall-bladder.

Case II.

The daughter of this patient, a housewife, aged 30 years, presented at the Royal Perth Hospital in December, 1956, with a history of right-sided upper abdominal pain of four months' duration. Born in Yugoslavia, she had been in Australia since the age of 12 years. Since childhood she had had attacks of jaundice associated with abdominal pain, nausea and the passage of dark urine lasting up to two months. Nausea and jaundice were also present during many of

her nine pregnancies. At the age of 22 years, because of severe pain and jaundice during pregnancy, cholecystography was performed at another hospital. After this she was submitted to laparotomy, and the gall-bladder, she understood, was drained. However, abdominal pain persisted, and a barium-meal X-ray examination revealed a gastric ulcer. With treatment of this her symptoms were relieved. At the age of 27 years, during the course of inquiry into her father's condition, she was thought to have familial acholuric jaundice. The serum bilirubin levels at this time were 0·9, 1·2 and 1·3 mg. per 100 ml. on three occasions. However,

TABLE I.

Investigations.	August, 1953.	November, 1955.	April, 1956.
Serum bilirubin level (mg. per 100 ml.)	2·6	4·5	3·6
Van den Bergh reaction ..	P[1]	P	P
Bile in urine	Present	Present	Present
Urinary urobilinogen excretion	Increased	Increased	Increased
Serum alkaline phosphatase content (King-Armstrong units)	7·4	4·6	2·7
Thymol turbidity (units) ..	1	1	1
Albumin (grammes per 100 ml.)	3·7	3·4	3·1
Globulin (grammes per 100 ml.)	4·6	3·2	3·0
Prothrombin time (normal, 12·5 to 14·5 seconds) ..	21	—	15

[1] P = immediate direct positive.

the serum alkaline phosphatase estimation and other tests of liver function gave normal results (see Table II), as also did the hæmoglobin estimation, reticulocyte count and erythrocyte fragility test.

The symptoms leading to her admission to hospital comprised pain in the right upper quadrant of the abdomen, radiating to the back and associated with flatulence and nausea. Icterus was not present. A barium-meal X-ray examination revealed a shallow ulcer on the greater curvature of the stomach, and oral cholecystography displayed a "non-functioning gall bladder".

Laparotomy was performed in January, 1957. The gall-bladder was absent, but a number of minute calculi were present in an elongated remnant of the cystic duct. This was excised. The common bile duct was normal, and the liver was described as being enlarged and dark in colour. After the operation jaundice reappeared, the serum bilirubin level two days later being 6·6 mg. per 100 ml. Throughout the next two weeks this gradually diminished, and she was discharged from hospital.

Four days later the patient was readmitted because of anorexia, vomiting, pain under the right costal margin and again jaundice. The liver was palpable 2 cm. below the costal margin. The urine contained bile, and urinary urobilinogen excretion was increased. The serum bilirubin level was 5·2 mg. per 100 ml., but the serum alkaline phosphatase estimation and other tests of liver function gave normal results (Table II).

During the following week the patient's jaundice intensified, and she remained miserable with anorexia and abdominal pain. The serum glutamic oxaloacetic transaminase level was elevated on two occasions, the maximum being 156 units (Table II). However, after this the jaundice gradually subsided. Hæmoglobin estimations, the reticulocyte count and measurement of the red-cell life gave normal results during this time, and the prothrombin time was 18 seconds (normal, 12·5 to 14·5 seconds). A liver biopsy performed during this admission showed the characteristic picture of the Dubin-Sprinz syndrome.

The patient was discharged from hospital in March, the serum bilirubin level then being 3·6 mg. per 100 ml.

TABLE II.

Investigations.	September, 1953.	February, 1957.	November, 1957.	July, 1958.	January, 1960.
Serum bilirubin level (mg. per 100 ml.)	1·2	5·2	2·7	1·6	1·3
Van den Bergh reaction	P[1]	P	P	P	P
Bile in urine ..	Absent	Present	Present	Absent	
Urinary urobilinogen excretion	Normal	Increased	Increased	Normal	
"Bromsulphthalein" retention (45 minutes)	—	—	16%	—	—
Serum alkaline phosphatase content (King - Armstrong units)	5	10·5	4·3	3	2·5
Thymol turbidity (units)	2	1	1	1	0
Albumin (grammes per 100 ml.) ..	4·0	4·8	3·7	3·1	—
Globulin (grammes per 100 ml.) ..	3·6	2·6	4·1	3·3	—
Serum glutamic oxaloacetic transaminase level	—	156	13	17	—
Serum cholesterol level (mg. per 100 ml.)	—	—	—	200	—
Prothrombin time (normal, 12·5 to 14·5 seconds) ..	—	18	—	14·5	—

P[1] = immediate direct positive.

She was readmitted in November, 1957, because of menorrhagia, for which hysterectomy was performed. At this time the serum bilirubin level was 2·7 mg. per 100 ml.; 1·3 mg. was of the direct-reacting type, and "Bromsulphthalein" retention was 16% after 45 minutes (normal, less than 5%).

The patient has continued to complain of weakness and attacks of abdominal pain, vomiting and jaundice. In July, 1958, she was reviewed because of severe backache, and in January, 1959, because of depression. Although jaundice has been overt only occasionally the serum bilirubin level has been persistently elevated (Table II). In March, 1959, the serum bilirubin level was 1·9 mg. per 100 ml.; 1·4 mg. was direct-reacting.

Histopathological Data.

Liver biopsy was performed in Case I in August, 1953, and in Case II in February, 1957. The discovery of the true nature of the illness after the latter biopsy led to a review of the former case and to the subsequent definitive diagnosis of Dubin-Sprinz syndrome. The findings in the two cases were as follows.

Case I.

On macroscopic examination, a tiny grey-brown cylinder of liver tissue was seen. The lobular architectural pattern was normally arranged. Many hepatic cells contained clumps of pigment appearing as dark golden-brown granules of varying size and staining intensity. This pigment was concentrated maximally in the centrilobular zones, and in the main was confined to parenchymal cells, although a few Kupffer cells were similarly affected (Figures I[1] to III). No marked degenerative

[1] For Figures I to IV see art-paper supplement.

change was apparent as a concomitant of the pigmentation, and the portal tracts were normal.

Case II.

The macroscopic appearance was similar to that in Case I.

Although the hepatic architecture was essentially normal, many hepatic cells contained clumps and granules of pigment with the same tinctorial characteristics as in the first case (Figure IV). A few hepatic cells were somewhat swollen and paler than normal. In the portal tracts a slight increase in the number of lymphocytes and macrophages was seen, together with an occasional polymorphonuclear leucocyte. The presence of fine lipid droplets within the hepatic cells was revealed by the Sudan IV stain.

In order to classify the pigment, a variety of histochemical procedures were performed (Table III). The pigment was found to be similar in nature to that described in the cases of Dubin (1958) and Taft and Earle (1959).

The presence of bilirubin and iron in the pigment was excluded by the results of the first three stains, and its lipochrome nature indicated by the Sudan Black B medium and the reactions with basic dyes and Schmorl's ferric ferricyanide. The pigment also exhibited similar characteristics to melanin, inasmuch as it was bleached by peroxide and was capable of effecting the reduction of silver.

Family History.

The family pedigree is shown in Figure V.

The first patient, father of the second patient, is one of seven siblings, none of whom is known to have suffered jaundice. He has five children and nine grandchildren. Serum bilirubin estimations and other biochemical tests of liver function have been performed on this patient's wife, on his son-in-law (the husband of the second patient), on all the remaining children and on eight of the grandchildren. His three sons were submitted to cholecystography.

Neither his wife nor his son-in-law has been jaundiced or has an elevated serum bilirubin level on one estimation. Of his five children, the eldest is discussed above (Case II). The second child, a female, now aged 23 years, gives no history of jaundice, and on one estimation the serum bilirubin level was normal.

There are three sons, aged respectively 20, 17 and 16 years. The eldest recalled two attacks of jaundice at the ages of six and 15 years, and he had two episodes in 1959, icterus lasting some two to three months in all. His serum bilirubin level was 0·9 mg. per 100 ml. in 1957, and an oral cholecystogram revealed only a faint shadow of the gall-bladder.

The second son, aged 17 years, has no symptoms and a serum bilirubin level of 1·5 mg. per 100 ml., and an immediate direct positive van den Bergh reaction was obtained. In addition there has been evidence of impaired excretion of urobilinogen and cholecystographic media.

The third brother is symptomless, with a normal serum bilirubin level and normal cholecystographic findings.

Of the nine children of the second patient (Case II), seven have normal serum bilirubin levels, one was not tested and one has a serum bilirubin level of 0·8 mg. per 100 ml. This daughter, aged 14 years, is symptomless, and bile has not been detected in the urine.

Discussion.

The two patients discussed appear to be suffering from chronic jaundice of the type described by Dubin and Johnson (1954) and by Sprinz and Nelson (1954), and reviewed by Dubin in 1958.

Both give histories of jaundice beginning at an early age, associated with abdominal pain, dark urine and hepatomegaly. The serum bilirubin level has been elevated and a direct van den Bergh reaction has been obtained. In addition, there has been evidence of impaired excretion of urobilinogen and of cholecystographic media. Liver biopsy has shown the characteristic histological findings, and "Bromsulphthalein" retention was increased in the second case, but was not estimated in the first.

The clinical findings and the results of laboratory investigations and liver biopsy have excluded such conditions as chronic hepatitis, hæmolytic anæmia and biliary obstruction as being the cause of the jaundice.

TABLE III.

Staining Reactions of the Hepato-Cellular Pigment.

Technique.	Dubin.	Taft and Earle.	Present Series.	
			Case I.	Case II.
Gmelin	Negative	Negative	Negative	Negative
Stein	Negative	Negative	Negative	Negative
Prussian blue	Negative	Negative	Negative	Negative
Scharlach-R	Variable	Negative	Negative	Negative
Sudan Black B	With prolonged staining, positive	30 min. staining, negative	Positive	Positive
Acid-fastness	Variable	Negative	Negative	Negative
Periodic acid-Schiff	Variable	Negative	Negative	Negative
Diamine silver reduction ..	Positive	Positive	Positive	Positive
Basic dyes: methylene blue, Sevki Giemsa, Mallory's basic fuchsin.	Positive	Positive	Positive	Positive
Schmorl's ferric ferricyanide ..	Positive	Positive	Positive	Positive
Peroxide bleaching	Positive	Positive 24 hours, 10% 30 vol.	Incomplete	Incomplete
Fluorescence (violet and ultraviolet light)	Dull brown	Dull brown	Dull brown	Dull brown
Polarized light	Isotropic	Isotropic	Isotropic	Isotropic
Fixation, paraffin (C and D, 5μ).	Masson's solution	Masson's solution	Carnoy	10% formol saline solution
Fixation, frozen sections (C and D, 15μ).	10% formol saline solution	10% formol saline solution	10% formol saline solution	10% formol saline solution
References	Pearse (1954)	Pearse (1954)	Culling (1957)	Culling (1957)

In the second case icterus was not recognized until after two operations on the biliary system. It is noteworthy that this patient has given birth to nine healthy infants and has had no miscarriages. Previous reports (John and Knudtson, 1956; Dubin, 1958) have stated that patients with this disorder commonly have abortions or give birth to children with congenital malformations.

Elevated serum levels of glutamic oxaloacetic transaminase were also found in this case, a finding not reported by other workers. It is probable that these levels were related to previous biliary tract surgery with superadded infection, and indeed the liver biopsy at this time revealed slight portal inflammation. Elevation of S.G.O.T. levels has been reported in association with cholelithiasis with concomitant inflammation (Madsen *et alii*, 1958).

In addition to these two cases, evidence is presented that two further members of the family suffer from the same disorder. These two, brothers of the second patient, had a history of icterus, or raised serum levels of bilirubin and/or abnormal cholecystograms. The radiological features of these cases have been reported previously (Hurst *et alii*, 1958).

The daughter of the second patient, aged 14 years, has not been included in the present report as being affected,

although her serum bilirubin level was in the upper range of normal.

Of the patients reviewed by Dubin (1958), 13 of 39 gave a family history of jaundice, and of these, two were siblings (John and Knudtson, 1956). Beker and Read (1958) described an affected mother and son, but two other children were normal. Recently Wolf *et alii* (1960) have reported two families suffering from chronic idiopathic jaundice, in one of which a mother and seven of 10 siblings were affected and in the other three of six siblings. Mandema *et alii* (1960) also record two afflicted families, one comprising an affected father and three of eight siblings and the other four of eight siblings. Although the number of cases is not great, the data in these and in the present family suggest that the disorder is inherited as a Mendelian dominant trait.

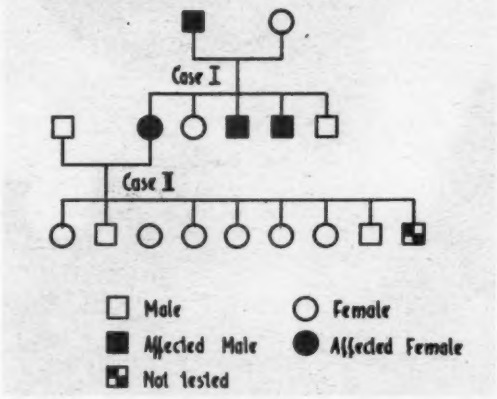

FIGURE V.
Family pedigree.

Histochemical studies indicate almost complete similarity of the pigment in these two cases and the two series outlined in Table III. A minor difference is that incomplete bleaching with peroxide occurred in our cases.

Investigation into the nature of the pigment has been outlined by Dubin in a review of the condition (1958). However, its exact composition is as yet unknown. Dubin believes the pigment to be related to the lipofuschin series because of its distribution and staining characteristics. By the same token there is a similar resemblance to melanin (Bynum, 1957), although melanuria is by no means a constant feature of the disease.

Taft and Earle (1959) have entertained the possibility that the pigment may be an insoluble and highly polymerized degradation product of hæmoglobin catabolism, thereby relating the material to the known biochemical lesion.

Recent knowledge of bilirubin metabolism has provided some understanding of the mechanism of the bile retention of chronic idiopathic jaundice, Gilbert's disease and related disorders.

It has been shown by Schmid (1956) and by Billing and Lathe (1956) that direct-reacting bilirubin is a glucuronide of bilirubin. In the excretion of bilirubin by the liver, the indirect-reacting bilirubin, which is water-insoluble, is conjugated with glucuronic acid to form the direct-reacting water-soluble bilirubin-glucuronide. This process involves the transfer of glucuronic acid from uridine-diphosphate-glucuronic acid to bilirubin, the enzyme involved being known as glucuronyltransferase. This is present in the microsomal fraction of liver homogenates. Arias and London (1957) have postulated that a deficiency of this enzyme is the basic defect in Gilbert's disease. Under these circumstances, the liver is unable to conjugate sufficient bilirubin with glucuronic acid, the remainder being retained in the plasma. This bilirubin gives the indirect van den Bergh reaction, and bile does not appear in the urine. It has also been considered that the defect in the infants described by Crigler and Najjar (1952) and in physiological jaundice of the new-born is due to a similar mechanism. However, recently it has been suggested that the primary defect in Gilbert's disease is related to a defective mechanism for transporting bilirubin from the plasma to the conjugating mechanism (Schmid and Hanmaker, 1959).

In chronic idiopathic jaundice the deficiency appears to be different. The direct-reacting form or bilirubin constitutes about 60% of the total elevation of the serum bilirubin level, so that conjugation with glucuronic acid can occur, and bile appears in the urine. The defect therefore appears to be in the further excretion of the bilirubin-glucuronide complex into the bile. Other excretory deficiencies also appear in this condition, as shown by the increased amount of urobilinogen in the urine, "Bromsulphthalein" retention, and inability to excrete radio-opaque dyes.

The patients described by Haverback and Wirtschafter (1960) resemble in some respects those described by Dubin. Points of similarity include the presence of conjugated bilirubin in the serum, retention of "Bromsulphthalein", and increased urinary urobilinogen excretion. However, liver biopsy and cholecystography failed to reveal any abnormalities.

The features of the two last-mentioned conditions suggest a familial inborn error in the metabolism of bilirubin and other substances.

Summary.

1. Two cases of chronic idiopathic (black liver) jaundice occurring in a father and daughter are presented, together with the findings in two further siblings who appear to have the same disorder.

2. A feature of one of the cases was the absence of any deleterious effect of the disorder on the offspring, in contrast to previous reports.

3. The relationship of the disorder to the other "congenital hyperbilirubinæmias" is discussed.

4. The importance of this group of conditions lies in their recognition and in the avoidance of needless surgery.

Acknowledgements.

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References.

ARIAS, I. M., and LONDON, I. M. (1957), "Bilirubin Glucuronide Formation in Vitro: Demonstration of a Defect in Gilbert's Disease", *Science*, 126: 563.

BEKER, S., and READ, A. E. (1958), "Familial Dubin-Johnson Syndrome", *Gastroenterology*, 35: 387.

BILLING, B. H., and LATHE, G. H. (1956), "The Excretion of Bilirubin as Ester Glucuronide Giving the Direct van den Bergh Reaction", *Biochem. J.*, 63: 6.

BYNUM, W. T. (1957), "Mavero-hepatic Icterus (Black Liver Jaundice)", *Gastroenterology*, 33: 97.

COMFORT, M. W., and HOYNE, R. M. (1944), "Constitutional Hepatic Dysfunction: Clinical Study of 35 Cases", *Gastroenterology*, 3: 155.

CRIGLER, J. F. jnr., and NAJJAR, V. A. (1952), "Congenital Familial Non-hæmolytic Jaundice with Kernicterus", *Pediatrics*, 10: 169.

DAMESHEK, W., and SINGER, K. (1941), "Familial Non-hæmolytic Jaundice: Constitutional Hepatic Dysfunction with Indirect van den Bergh Reaction", *A.M.A. Arch. intern. Med.*, 67: 259.

DUBIN, I. N., and JOHNSON, F. B. (1954), "Chronic Idiopathic Jaundice with Unidentified Pigment in Liver Cells: New Clinicopathologic Entity with Report of 12 Cases", *Medicine*, 33: 155.

DUBIN, I. N. (1958), "Chronic Idiopathic Jaundice: Review of Fifty Cases", *Amer. J. Med.*, 24: 268.

GILBERT, A., LEREBOULLET, P., and HERSCHER, M. (1907), "*Les trois cholémies congénitales*", *Bull. Soc. med. Hôp. Paris*, 24: 1203.

HAVERBACK, B. J., and WIRTSCHAFTER, S. K. (1960), "Familial Non-hæmolytic Jaundice with Normal Liver Histology and Conjugated Bilirubin", *New Engl. J. Med.*, 262: 113.

HURST, P., LITTLE, J. H., and VAUGHAN, B. F. (1958), "The Cholecystogram in Chronic Idiopathic Jaundice", *Proc. Coll. Radiol. Aust.*, 2: 102.

JOHN, G. G., and KNUDTSON, K. P. (1956), "Chronic Idiopathic Jaundice: Two Cases Occurring in Siblings with Histochemical Studies", *Amer. J. Med.*, 21: 138.

MADSEN, S., BANG, U. N., and IVERSON, K. (1958), "Serum Glutamic Oxaloacetic Transaminase in Diseases of the Liver and Biliary Tract", *Brit. med. J.*, 1: 543.

MANDEMA, E., DE FRAITURE, W. H., NIEWEG, H. O., and ARENDS, A. (1960), "Familial Chronic Idiopathic Jaundice (Dubin-Sprinz Disease), with a Note on Bromsulphthalein Metabolism in this Disease", *Amer. J. Med.*, 28: 42.

ROTOR, A. B., MANAHAN, L., and FLORENTIN, A. (1948), "Familial Non-hæmolytic Jaundice with Direct van den Bergh Reactions", *Acta med. Philipp.*, 5: 37.

SCHMID, R. (1956), "Direct Reacting Bilirubin, Bilirubin Glucuronide, in Serum, Bile and Urine", *Science*, 124: 76.

SCHMID, R., and HANMAKER, L. (1959), "Glucuronide Formation in Patients with Constitutional Hepatic Dysfunction (Gilbert's Disease)", *New Engl. J. Med.*, 260: 1310.

SPRINZ, H., and NELSON, R. S. (1954), "Persistent Non-hæmolytic Hyperbilirubinæmia Associated with Lipochromic-like Pigment in Liver Cells: Report of Four Cases", *Ann. intern. Med.*, 41: 952.

TAFT, L. I., and EARLE, E. (1959), "Black Liver Jaundice Diagnosed by Needle Biopsy", MED. J. AUST., 1: 486.

WOLF, R. L., PISETTE, M., RICHMAN, A., DREILING, D. A., JACOBS, W., FERNANDEZ, O., and POPPER, H. (1960), "Chronic Idiopathic Jaundice. A Study of Two Afflicted Families", *Amer. J. Med.*, 28: 32.

INTRAORAL REMOVAL OF ADAMANTINOMA.

By J. M. FOREMAN, F.R.C.S.,
Lautoka Hospital, Lautoka, Fiji.

Only the smallest adamantinomas can be removed by way of the mouth.—Aird (1957).

THIS is hardly correct, and in this connexion a relevant case report is produced. Adamantinoma is not a common condition — for instance, only four cases presented over a five-year period at the Royal Adelaide Hospital (Hamilton, 1959) — and thus edicts in management are probably copied from book to book rather than derived from personal experience. Further, the condition to some extent falls in that "no man's land" between medicine and dentistry, so that treatment tends to be inconsistent and sometimes inadequate. In fact, there may even be muddled thinking in the matter of management; for instance, "The tumour is benign but is very prone to recur locally after removal and even after several operations" (Stones, 1951). How can a tumour be benign and show such marked tendency to recurrence?

It is becoming increasingly realized that resection of the affected portion of the mandible as first recommended by Ivy and Curtis (1937) is justified, curettage with or without diathermy of the wall of the cavity being followed almost inevitably by recurrence of the tumour. In fact, in the great majority of case reports of adamantinomas there is a history of previous inadequate surgery.

American authorities — for example, Ward and Hendrick (1950*a*)—suggest early resection of the affected portion of the mandible, whereas British authorities are more conservative and recommend that resection be used only for recurrence of the tumour. However, if it is agreed that adamaninoma is histologically and in its behaviour (locally malignant) akin to basal-cell carcinoma of the skin (Aird, 1957), then surely the only safe and certain method of treatment is resection of the affected portion of the mandible, or possibly, if the tumour is very small, resection of the tumour with a margin of 1 cm. of normal tissue, the lower border of the mandible being left intact.

Clinical Record.

A, a Solomon Islands female, aged 29 years, was referred to the surgical unit of the Lautoka Hospital by a dental officer on January 23, 1960, on account of a large central adamantinoma, suggested by X-ray examination (Figure I) and proved by biopsy. The dental officer had carried out a biopsy and curettage several months previously, but the tumour had continued to

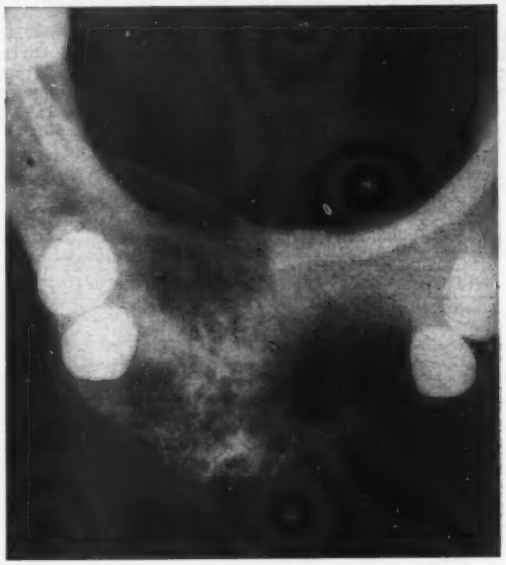

FIGURE I.

grow and was causing increasing pain. It was felt that resection of the affected portion of the mandible was now called for, and the thing to decide was the best surgical approach to the tumour.

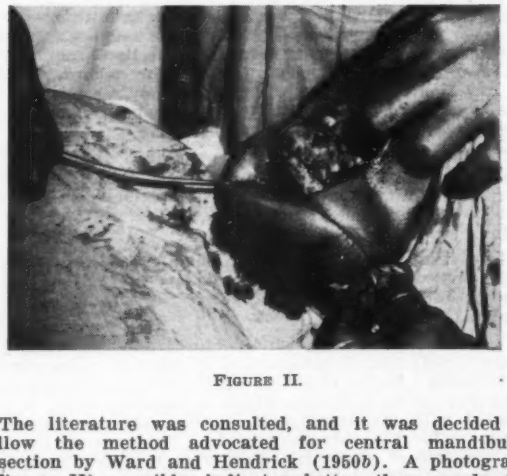

FIGURE II.

The literature was consulted, and it was decided to follow the method advocated for central mandibular resection by Ward and Hendrick (1950*b*). A photograph (Figure II) possibly indicates better than words the approach; at this point the Gigli saw was in position to divide the left side of the mandible, the lower lip and related soft tissues having been turned down off the mandible through mobilization in the subperiosteal plane. The central part of the mandible having been resected, and the bone ends smoothed off, buccal to lingual mucosa closure was performed, with care to avoid the subman-

dibular and sublingual ducts. This approach gave an excellent exposure and must surely be satisfactory for all central adamantinomas, apart from the very largest.

The patient's further progress has been satisfactory, and she is wearing upper and lower dentures which are most effective, both functionally and cosmetically.

Acknowledgement.

I wish to thank Dr. P. W. Dill Russell, C.B.E., Director of Medical Services, Fiji, for permission to publish this report.

References.

AIRD, I. (1957), "Companion in Surgical Studies", Livingstone, Edinburgh and London: 290.

HAMILTON, I. (1959), "Extensive Adamantinoma and Other Tumours of the Jaw", MED. J. AUST., 1: 802.

IVY, R. H., and CURTIS, L. (1937), "Adamantinoma of Jaw", *Ann. Surg.*, 105: 125.

STONES, H. H. (1951), "Oral and Dental Diseases", Livingstone, Edinburgh and London: 840.

WARD, G. E., and HENDRICK, J. W. (1950), "Tumours of the Head and Neck", Williams & Wilkins, Baltimore: (a), 319; (b), 338.

Reviews.

Lectures on the Interpretation of Pain in Orthopedic Practice. By Arthur Steindler, M.D. (Hon.), F.R.C.S. England), (Hon.), F.R.S.M. (England), F.A.C.S. (Hon.), F.I.C.S., with Anatomical Dissections by Dr. Rodolfo Cosentino, 1959. Springfield, Illinois: Charles C. Thomas, Publisher. Oxford: Blackwell Scientific Publications Ltd. 10" × 6¼", pp. 752, with many illustrations. Price: £7 8s.

MOST AUTHORS would be content to publish one volume of this nature in their lifetime. Not so Dr. Arthur Steindler, for this represents his eleventh text on orthopædic surgery and was produced just before his death in 1959 at the age of 79 years. Unlike some of his earlier writings, it is very readable, and indeed, as the pages unfold, the reader is fascinated by the author's searching inquiry for the truth, and his explanation and interpretation of many phenomena which are often taken for granted or more simply passed over.

The nature, quality, distribution and temporal relationship of pain in all parts of the body are analysed, and the reader is taught how this knowledge can be used in diagnosis, treatment and even prognosis. Early chapters are devoted to the anatomical and physiological background of pain, and there follow the most erudite discussions of pain in joints, in bones, in ligaments and so on.

Succeeding chapters deal with the pain syndrome in the anatomical sites of the body, and one very noteworthy chapter is that concerned with sorting out all those difficult sources of pain at the cervico-brachial junction.

The book is well set out and well illustrated, but has to be taken in relatively small doses, for the text requires much thought and digestion. Steindler wrote in the preface of an earlier text: "There will always be those who are anxious to find a short cut to results and in their hurry pass by the stations of diagnosis and indications, making specific operative surgery as their first step. No doubt they will be disappointed." He must also have had this volume in mind when he wrote this, for no orthopædic surgeon could fail to benefit by reading it.

Only two criticisms can be offered. First, the English reader will find a bewildering variety of new "orthopædic" words, whose meaning can therefore only be guessed. Secondly, the price seems very excessive even by present-day values.

Handbook of Hæmatological and Blood Transfusion Technique. By J. W. Delaney, F.I.M.L.T.; 1960. London: Butterworth & Co. (Publishers) Ltd. 8½" × 5¾", pp. 150, with illustrations. Price: 62s. 6d.

THE avowed purpose of this book is to assist candidates sitting for the examinations of the Institute of Laboratory Technology, London. The author is Chief Technician, Vincent Square Laboratories of the Westminster Hospital, London, and an examination assessor of the Institute. He has the gift of concise and lucid writing and has succeeded in producing an extremely useful laboratory handbook.

The first section deals with hæmatological and the second with blood transfusion techniques, and although theoretical considerations are discussed, this is on the whole a purely practical work. Indeed, its great virtue lies in the comprehensive range of techniques and formulæ provided between its covers. Most techniques are set out in a step-by-step fashion. In some places, when he is dealing with more complex techniques, such as those concerned with the investigation of coagulation disorders, this approach is perhaps not adequate, and more detailed discussions of the possible sources of error might have been of advantage.

The book contains a number of loose statements, which are perhaps the result of attempts at over-conciseness of expression. Thus, it is stated (page 231) that it is necessary to genotype all Rhesus-negative individuals. This is, surely, not what the writer meant. What is necessary is that all D-negative blood donors be tested for the C and E antigens. Likewise the definition of an anamnestic reaction (page 203) is actually that of a so-called non-specific anamnestic reaction. Although in the same paragraph the author describes the more important type, the specific anamnestic reaction—that is, the accelerated antibody production after a second injection of an antigen—it is not included in the definition. The statement (page 211) that chimerism is found in uniovular twins is incorrect. The rule attributed to Landsteiner in the book (page 117) is credited to Ehrlich by most serologists, who usually reserve the name "Landsteiner's Law" for the serological axiom that if an antigen of the ABO system is lacking on the cells, the equivalent antibody will be found in the serum.

These criticisms, however, concern points of theory, and do not detract from the practical usefulness of the book.

Artefacts and Handling and Processing Faults on X-ray Films. By Prof. Dr. E. A. Zimmer; 1960. New York and London: Grune & Stratton. 9½" × 6¾", pp. 72, with 128 figures. Price: $5.75.

THIS small volume contains 128 illustrations of artefacts which may occur on X-ray films with accompanying explanatory legends. It is a fairly complete collection and is, therefore, of value to those whose work interests them in this subject. The illustrations are of good quality and the text is concise and informative.

Introduction to Health Statistics: For the Use of Health Officers, Students, Public Health and Social Workers, Etc. By Satya Swaroop, M.A., Ph.D., M.P.H., F.N.I.; 1960. Edinburgh and London: E. & S. Livingstone, Ltd. 9¼" × 6", pp. 364, with tables and diagrams. Price: 40s. net (English).

SWAROOP, Chief Statistician of the Health Statistical Methodology Centre of the World Health Organization, Geneva, has written this introduction to health statistics. Successive chapters of the first part set out the role of statistics in public health, what basic data to collect, the population census, vital statistics, notifiable diseases, morbidity statistics, family health records. These are the foundations. Then are discussed health statistics and the world, legislation, record card systems and statistics in health departments in a part on administration. The third part deals with statistical classification, processing and analysis, mortality and fertility rates, morbidity, life tables, diagrams, evaluation. Finally there are some tables and recommendations of the World Health Organization and an index and bibliography.

The book has some interesting tables and graphs, but is really too long for its depth. A book of this size should have mentioned generation rates, especially since fertility and tuberculosis are discussed. There is a great deal of padding. However, the book will be of value to public health workers and students.

Babies and Young Children: Feeding: Management: Care. By Ronald Illingworth and Cynthia Illingworth; Second edition; 1960. London: J. and A. Churchill, Limited. 8¼" × 5¼", pp. 339, with 23 plates and many illustrations. Price: 18s. (English).

THIS is the second edition of this excellent book for parents. It deals with the feeding, management and care of babies and young children, and covers physical and emotional needs. It is full of common-sense and practical help that all parents will welcome. There are sections on sleep, feeding, toilet training, toys and play, accident prevention, and some common and important symptoms. A book by such authorities as the Illingworths can be accepted as reliable; but it adds to its value that the Illingworths

have had to practise what they preach and apply it to their own family life, so introducing a sympathetic and human note that is not always apparent in a book for parents. The book is easy to read, encouraging and comforting, besides being just sufficiently light to avoid adding any anxiety to apprehensive parents.

We consider this book preferable to, and more acceptable to Australian readers than, "Baby and Child Care" by Benjamin Spock. Unfortunately it is much more expensive. However, it can be recommended with enthusiasm, and it is to be hoped that many doctors will buy it for their wives and lend it to their patients. Health centre sisters will find it most useful and well worth acquiring.

Hospital Infection: Causes and Prevention. By R. E. O. Williams, M.D., M.R.C.P., *et alii*; 1960. London: Lloyd-Luke (Medical Books) Ltd. 8¼" × 5½", pp. 318. Price: 35s. net (English).

AT a time when increasing interest is being taken in infections contracted in hospital, the publication of this book will be welcomed by all concerned with their control. The authors write with the authority of many years of investigation in English hospitals, and also with much common sense regarding the measures to be taken if we are to hope to reduce the incidence of these infections.

The book is divided into two parts, implicit in its title, the first part dealing with the epidemiology of hospital infections and the second with their control. In their preface the authors state that they anticipate the criticism that too much space is devoted to staphylococcal infection, but justify themselves, correctly, on the grounds that this infection, in its protean forms, has caused much alarm and perplexity in recent years. In the section on epidemiology, therefore, there are three chapters on various aspects of staphylococcal infection. Other chapters deal with hæmolytic streptococci, with the clostridia and with miscellaneous infections. In addition there are chapters on urinary tract and gastro-intestinal infections and on sepsis due to Gram-negative bacilli. The reservoirs and likely routes of infection are discussed, and attention is paid to patients who may be at special risk.

In the section on control, the duties of a control-of-infection officer are set out, and the value of proper sepsis records is stressed. The design of operating theatres is discussed in some detail, particularly their ventilation. Methods of control of infection in wards under such headings as segregation, prevention of self-infection and of infection by the hospital staff, and environmental contamination are fully discussed. There are chapters on the principles and methods of sterilization by heat and by chemicals. Of particular value to nursing staff and bacteriologists may be the chapter which gives practical information on the sterilization of an alphabetical list of articles ranging from air to water closets.

Every surgeon, pædiatrician, medical superintendent, matron and hospital bacteriologist should carefully assimilate the information in this book, and then make it their immediate task to assess critically, in the light of this knowledge, the practices in their own hospitals. There is no panacea for the cure of hospital ills. Improvement will follow only by close and continuous attention to multitudinous details.

An Introduction to Functional Histology. By Geoffrey H. Bourne, M.Sc., D.Sc., D.Phil.; Second edition; 1960. London: J. & A. Churchill Ltd. 9" × 6¼", pp. 212, with 181 illustrations. Price: 32s. net (English).

THE author's stated aim has been to produce a textbook that should form useful supplementary reading for graduate students in biological sciences and for medical and dental students. Its chief value, in fact, resides in its often stimulating presentation of histochemical findings, particularly those of the author and his collaborators. However, the major part of the text forms little more than a threadbare cloak loosely draped over an incomplete infant skeleton of histochemical results.

There are many errors, of which a few from a very small section of the book dealing with nervous tissue may serve as illustration. Statements appear that the distance between nodes of Ranvier is related to the length of nerve fibres, that the application of a one-pound pressure to a peripheral nerve induces no microscopically visible degenerative change in the nerve fibres, and that, in the process of regeneration, it does not matter functionally if an axon does not reach its original neurilemmal tube; the descriptions of the muscle spindle and the motor end-plate are grossly inadequate for "functional" interpretation.

The author does poor service to the sister science of macroscopic anatomy by such statements as that the tonsil is near the junction of the pharynx and œsophagus, that a long bone possesses two heads, and that the whole of the alimentary tract excluding the œsophagus is covered with peritoneum. The text frequently lacks descriptive clarity, and its grammatical construction is sadly inelegant.

Inevitably, because of the errors and the unbalanced presentation, this book is unsuitable for undergraduate medical and dental students. The discriminating graduate in the biological sciences may be able to sift the errors and redundancies from the core of histochemical data, but he will be disappointed to find no references to original papers. Since many of the facts are presented in a brief, didactic fashion and with very little discussion of their significance, omission of references will be doubly felt. Reluctantly, the conclusion is advanced that the excellent prospects opened up by the title of this book have not been realized. It is too unbalanced and unreliable for undergraduate reading, and it does not give the depth of treatment required by the graduate student.

An Introduction to Pharmacology. By J. J. Lewis, with a foreword by Stanley Alstead, C.B.E., M.D., F.R.A.C.P. Edin., F.R.C.P. Lond., F.R.F.P.S.; 1960. Edinburgh and London: E. & S. Livingstone, Ltd 8¼" × 5½", with 163 figures and 28 tables Price: 55s. (English).

TEN YEARS AGO, the number of textbooks of pharmacology in the English language could almost be numbered on the fingers of one hand; but today about half a dozen new texts appear every year. There are two reasons for this; the first and most striking is the rapidity of change in drug therapy as a result of the intensive development of new medicaments; the second, presumably, is the author's belief that his students are not adequately provided for by existing works. The author of this book states that his purpose was to give a scientific treatment to the elements of the subject, and not to provide a textbook of materia medica or therapeutics or to describe the treatment of diseases by the drugs he discusses. This is quite a substantial book, and comprises some 36 chapters, so that the coverage of both new and old drugs is almost complete.

The first half of the book deals with symptomatic drugs and the latter part with chemotherapy. In this field the author has hardly kept up with his intentions, since he devotes well over 100 pages to the chemotherapy of all types of infections, and the scientific basis for the action of these drugs takes a secondary place.

The vitamins and hormones are dealt with only briefly because, we assume, these drugs are presumed to be adequately dealt with in biochemical texts. However, it does present a gigantic task to dispose of all these substances in one chapter.

Each chapter is liberally illustrated with chemical formulæ and the relationship of one drug to another is clearly illustrated.

This is a very useful book without a doubt, and it will be attractive to pharmacists because it gives a succinct account of each drug and its mode of action. Again, it will provide a useful background for the general practitioner. For the student of pharmacology, as a true science, it is inadequate, since it does not give references, and the inclusion of such a complete range of drugs precludes the presentation of any considerable detail about each.

We might criticize a few statements scattered throughout the book, which do not give the latest ideas on the mode of action of a number of drugs—as, for example, ephedrine and reserpine; but generally the book gives a very fair, if brief, summary of our present knowledge of how drugs act. The book is well produced and attractively written, and is remarkably free of errors, although the habitual misspelling of carbamylcholine still persists. To sum up, this is a book which can be thoroughly recommended to pharmacists and the busy practitioner who still likes to be able to look up the scientific basis for his treatments.

The Tonsils and Adenoids in Childhood. By Donald F. Proctor, M.D.; 1960. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 11" × 8½", pp. 84, with illustrations. Price: 60s. (English).

IT would appear that this book was written in answer to a challenge by a colleague, who roundly condemned tonsillectomy as a useless procedure responsible for the deaths of 300 Americans annually. Dr. Proctor answers critics in the final chapter of his book, by a comment to the effect that shortcomings are a reflection on the surgeon, and not

on the operation itself. He analyses the results of 261 operations carried out by himself, and these are in contrast to analyses which involve thousands of operations carried out by all and sundry, trained and untrained.

The tonsil operation is one of the first taught. Regarded as being within the province of most who enter practice, it is, however, too frequently performed in a manner which reflects no credit on the surgeon or on his training. This book of 70 well-illustrated pages will provide profitable and easy reading for all who intend to operate on tonsils.

The opening chapter is an entertaining history of tonsillectomy, and from this the author proceeds through morbid anatomy, indications for operation and anæsthesia to the operation itself, concluding with complications and their management, and end results.

Some of Dr. Proctor's indications for operation, invite criticism, and examinees would court disaster in our medical schools, if "asthma" was mentioned. Not everybody would agree that removal of the large hyperplastic tonsil is "seldom necessary".

The treatment of adenoids is well covered; but the frequent presence of tenacious fluid in cases of tubotympanic catarrh prompts the view that the author's results in the management of deafness in children would be improved if he practised the myringotomy and aspiration which he suggests are not necessary.

Adenoidectomy alone was carried out in 7% of cases. This figure appears excessively low.

Dr. Proctor has not been called upon to resuture in a single case of bleeding in 1202 consecutive operations. Two patients required blood transfusion. These results of his skill and his good fortune may be misleading to the uninitiated.

The book is well worth the attention of a critical reader, who no doubt would like to see some credit given to Boyle for the development of his gag.

Behavioural Change in the Clinic—A Systematic Approach. By Gerald R. Pascal, Ph.D.; 1959. New York and London: Grune and Stratton Inc. 8¼" × 5", pp. 136, with illustrations. Price: $4.75.

THIS book makes one or two interesting statements about stress and its role in the development of mental illness and deviant behaviour. Pascal first defines stress as deprivation of one of the basic physiological needs, and then enlarges it to cover frustration of an expected satisfaction. He postulates a hierarchy of stress-producing situations, in which behaviour can be altered by a more "pre-potent" stress crowding out a less "pre-potent" one. Under "Stress" and "Habit" there are some interesting observations from a behaviourist who is not to be outdone in psychopathology by the various dynamic contenders.

Pascal writes: "The present work is an attempt to apply the scientific method to the problem of changing gross human behaviour." He goes on to arouse the hope that he will show us again how the methods of the experimental psychologist can be applied to the solution of our clinical problems; but the hope is not fulfilled. He describes the administration of massive doses of T.L.C. (tender loving care to the uninitiated) as a softening-up for psychotherapy. He treats us to an elaborate and complicated statement of the fact that the psychotherapist fills a projected role in relation to the patient. He makes other unoriginal observations, and he gives us symbols and equations to prove his point. But such a precipitous and premature venture into symbolic language can create a dangerous illusion of scientific precision and raise barriers in communication.

"Somewhere between the obscure and the obvious", if it is fair to quote Pascal against himself, is a fair description of this book.

A Biochemical Approach to Pathology. By M. J. R. Dawkins, M.B., B.Ch., M.R.C.P., and K. R. Rees, M.Sc., Ph.D.; 1959. London: Edward Arnold (Publishers) Ltd. 8½" × 5½", pp. 138, with 30 illustrations. Price: 18s. (English), Australian price: 33s. 6d.

THIS short book in seven chapters concisely elucidates some of the contributions biochemistry has made and will make to pathology. There is a clear description of the fundamentals of cell metabolism, and a chapter on subcellular organization that emphasizes the importance of intracellular enzyme location. If the book is ever enlarged, then this is the part to extend.

A section on "Model Systems in Experimental Pathology" uses such examples as carbon tetrachloride poisoning, and cites the evidence supporting the particular kind of mitochondrial injury that it is thought to produce. Another example used is thioacetamide poisoning and the increasing intracellular level of calcium it produces. This is of particular interest, in view of recently demonstrated increase of hepatic calcium levels with other hepatic poisons.

Fluoracetate tricarboxylic acid cycle jamming is a classical example cited of lethal synthesis.

A section on endogenous poisons encountered in human pathology follows logically; kernicterus, 2,4-dinitrophenol and bacterial toxins are among those discussed. The chapter on deficiency states is a little disappointing, but it is one of the most difficult sections of biochemistry to present and it is clearly impossible to satisfy all. The chapter on "Genes, Enzymes and Disease" is very good. A few may disagree with one or two details, but for the book's purpose it is satisfactory. The book finishes with a short chapter on cell growth. All in all, this is an excellent book, which should be read by all clinical pathologists and particularly by those with an academic interest in their subject.

Individualtherapie und Prophylaxe der hysterischen, anankastischen und sensohypochondrischen Neurosen. By Karl Leonard, 1959. Jena: Veb Gustav Fischer Verlag. Sydney: Angus & Robertson Ltd. 8½" × 6", pp. 80. Price: Brosch. DM6.35.

THIS is one of a series of handbooks on various aspects of psychiatry and neurology written for the general physician. The author places special emphasis on an assessment of the psychoneurotic's personality in addition to the recognition of his particular symptoms as a necessary basis for sound and effective therapy. The syndromes described fall for the most part within the categories of what British psychiatrists term anxiety hysteria or anxiety neurosis. Professor Leonard observes that hysteria comes under notice far more frequently under the guise of somatic symptoms than in the form of the florid presentations which were demonstrated by Charcot in his "circus". The obsessional can often be weaned successfully from his fears if the physician is prepared to encourage him to handle sharp objects, stand by his side when looking down from a height, or travel up and down in lifts with him, procedures which the author is able to entrust to a team of assistants. The senso-hypochondriacs are comprised of two groups—(*a*) those with morbid, obsessional fears about health and (*b*) those with a heightened awareness of organic sensations. Depressive reactions must be excluded. The author makes no reference to those bizarre somatic symptoms which point to schizophrenia. Prophylaxis, in his view, depends on early recognition and correct handling from the start.

The author has avoided committing himself to advice about the absolute prevention of psychoneurosis. The general physician is not expected to attempt any "depth-analysis", which is regarded as actually harmful in the majority of the syndromes dealt with in this book. There is no reference to pharmacotherapy, and the psychotherapy favoured consists of a mixture of persuasion, suggestion, exhortation and guidance, in proportions which appear suitable for any particular case.

Kinesiology and Applied Anatomy: The Science of Human Movement. By Philip J. Rasch, Ph.D., C.C.T., F.A.C.S.M., and Roger K. Burke, Ph.D., F.A.C.S.M., 1959. Philadelphia: Lea and Febiger. Sydney: Angus and Robertson Limited. 9¼" × 5¾", pp. 456, with 226 illustrations. Price: 82s. 6d.

KINESIOLOGY is the somewhat pretentious name recently applied to the study of human movement; it consists of material selected from the anatomy and physiology of the locomotor system plus a certain amount of elementary mechanics. This combination finds its chief application in the curricula of students of physiotherapy and physical education, and this book is intended for them and for athletic coaches and trainers. It begins with a brief discussion of the structure and functioning of the locomotor system, the emphasis being upon muscle; this is followed by three chapters on mechanical principles. The main part of the book consists of an account of the movable joints of the body, again chiefly from the point of view of the actions of the muscles which move them. There is a discussion on posture, and on walking, running and jumping, and the book ends with two chapters on sports and games and the use of the locomotor system in everyday life.

When one considers the audience for whom it is intended, there are some curious omissions and inclusions. For example, it is difficult to see the value of a knowledge of

the serratus posterior superior or the spinalis cervicis to an athletic coach or even a physiotherapist; yet these and other insignificant muscles are accorded equal typographical rights with vital muscles such as the rectus abdominis. On the other hand, muscle tone is not discussed adequately, and the discussion of the lower limb, which one would expect to find treated very fully in a book of this kind, is disappointing in comparison with the rest of the body. It is difficult to see why the illustrations (borrowed from Gray) showing the origins and insertions of muscles should be relegated to an appendix rather than included in the body of the text, where they would be more useful. The movements of the hand are described in a way which is bound to cause confusion; for example, the abductor pollicis brevis is said to flex the thumb and the abductor digiti quinti to adduct the little finger. There are several misprints and a number of textual slips; the index is inadequate. Nevertheless, this is probably a useful introductory account, and this opinion is borne out by the fact that it is in effect a new edition of a book which has already gone through seven previous ones.

Lecture Notes on Ophthalmology. By Patrick D. Trevor-Roper. 1960. Oxford: Blackwell Scientific Publications. 7" x 4¼", pp. 100. Price: 12s. 6d.

THIS is a most unusual little book, designed to assist the harassed final-year student. It contains only 90 pages, in which are squeezed eight chapters, and is illustrated by 76 diagrams, many of which appear in colour. Chapter I is labelled "Introduction", but it contains a description of the eyeball and its contents and a brief description of methods of examination. Chapter II, on the eyelids and the lachrymal and orbital tissues, covers an amazing field in 15 pages and a similar number of diagrams. Squint receives a chapter of its own. The chapter on painful red eye discusses conjunctivitis, iritis, acute glaucoma, keratitis and scleritis. The next chapter is on gradual loss of sight in quiet eyes, in which the author discusses cataract, simple glaucoma, retinal and choroidal degeneration and diseases of the optic nerve; this is a most unusual and refreshing grouping of ocular diseases. Chapter VI, on sudden loss of sight in quiet eyes, describes the various retinopathies, central artery occlusion, venous occlusion, retinal detachment and retinal and choroidal tumours. The final two chapters are concerned with injuries and refractive errors.

This small book will probably enjoy a wide circulation among harassed final-year students, for whom it was written.

Surgery and Clinical Pathology in the Tropics. By Charles Bowesman, O.B.E., B.A., M.D., F.R.C.S.E., F.A.C.S., D.T.M. & H., E.D.; 1960. Edinburgh and London: E. & S. Livingstone Ltd. 9¾" x 6", pp. 1076, with 321 illustrations. Price: £5 10s.

A RECENT CONVERSATION with a surgeon practising in the tropics left us with the firm impression that his work was little different from that with which we have to contend in higher latitudes. It is true that it did not quite seem to be our surgery, simply practised in a hotter environment, for he took it for granted that air-conditioning would be the rule.

However, it is clearly apparent that there is a different side to the picture, and this is the one which must prevail—the practice of surgery under the most trying circumstances, with indifferent help, and against the background of malnutrition, malaria and infestation by parasites, and with the added hindrance that comes from racial and religious prejudice. The surgeon working in this environment must be jack-of-all trades, resourceful, patient and schooled to do many different things with the minimum of help and equipment. Whatever his natural ability, his competence in this varied type of practice is certain to be, in large part, a measure of his experience. But for a young man let loose on his own under such circumstances, this must be a disturbing state of affairs, even in a community where he can only hope to do the best of which he is able. If this volume faithfully represents the kind of problems with which the surgeon in the tropics will be called upon to contend, and we are sure that it does, it is quite apparent that a shelf of the standard texts (even if they are proofed against the ravages of ants and borers) will be a source of little comfort. One suspects that Bowesman will be able to give the answers to many of his most vexing and urgent questions, for this is quite an extraordinary book. It is a massive text, almost encyclopædic in its completeness. It is, however, at the same time infuriatingly discursive and disorderly. It would take a long time to find one's way through its thousand pages, but the experience would certainly be an enjoyable one.

The style is curiously mixed; sometimes friendly and almost conversational, where it gives a clinical illustration from a rich experience; at others formal and distant, where it catalogues the work of others (for it enjoys an extensive bibliography). Whatever the style, however, one is always conscious that the author is everywhere striving to be helpful, and in this it is certain that he will succeed. Inclusion of clinical pathology in the title is amply justified, for disease as it presents in these pages is often pathology in its most gross and distorted forms, and it is, moreover, pathology in its most exciting, varied and exotic manifestations. Malaria, sickling, worms, schistosomiasis, the ritual operations on the genitals, obstructed labour, scorpions and snakes and ophthalmology—they come tumbling one after the other in a bewildering succession that makes nonsense of the experience of those of us who were once proud to call ourselves general surgeons.

Here is an exciting and intensely interesting book, which the eager young man beginning his assignment in the tropics will enjoy immensely (although we suspect that he must not take it too seriously), when he seeks the solace of the punkah in the stillness of the tropical evening. We shall be surprised if, when later on he has acquired the confidence that comes from experience, we do not find in a position of prominence in his place of work a well-thumbed and well-worn copy of this remarkable book. It may well become a classic.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Medicine: A Lifelong Study": Proceedings of the Second World Conference on Medical Education, under the auspices of The World Medical Association; 1961. New York: World Medical Association. 9¼" x 6", pp. 824. Price: £5 5s. net (English).

"Tumors of the Female Sex Organs, Part III: Tumors of the Ovary and Fallopian Tube", by Dr. A. T. Hertig, M.D., and H. Gore, M.B., B.S.; 1961. Washington, D.C.: Armed Forces Institute of Pathology. 10¼" x 8", pp. 176, with many illustrations. Price: $1.40.

"Laennec: His Life and Times", by R. Kervran, M.D., translated from the French by D. C. Abrahams-Curiel; 1960. Oxford, London, New York, Paris: Pergamon Press. 8¼" x 5¼", pp. 220. Price: 21s. net (English).

"Growing Old: Problems of Old Age in the Australian Community", edited by Alan Stoller; 1960. Melbourne: F. W. Cheshire Pty. Ltd. 8¼" x 5¼", pp. 212. Price: 15s.

"Anatomy and Physiology for Nurses", by W. P. Gowland, M.D. (Lond.), F.R.C.S. (Eng.), and J. Cairney, C.M.G., D.Sc., M.D., F.R.A.C.S.; sixth edition; 1961. Christchurch: N. M. Peryer Ltd. 8¼" x 5¼", pp. 534 with illustrations. Price: 45s. (New Zealand).

"Gynæcology for Senior Students of Nursing", by J. Cairney, C.M.G., D.Sc., M.D., F.R.A.C.S.; second edition; 1961. Christchurch: N. M. Peryer Ltd. 8¼" x 5¼", pp. 225 with illustrations. Price: 30s. (New Zealand).

"Electron Microscopy in Anatomy: Proceedings of a Symposium held by the Anatomical Society of Great Britain on the Ultra-Structure of Cells", introduced by J. Z. Young; 1961. London: Edward Arnold Ltd. 9¼" x 6", pp. 296 with illustrations. Price: 50s. net (English).

"The Closed Treatment of Common Fractures", by J. Charnley, B.Sc., M.B., F.R.C.S.; third edition; 1961. Edinburgh, London: E. & S. Livingstone. 9¾" x 6¾", pp. 282 with many illustrations. Price: 50s. net (English).

"Salmonella; Salmonella Infections: Bibliography of Literature 1955-April, 1960", compiled by Dorothy Bocker, M.D.; 1960. Washington, D.C.: U.S. Department of Health, Education, and Welfare. 9¼" x 6", pp. 46. Price not stated.

"The National Library of Medicine Index Mechanization Project", *Bulletin of the Medical Library Association*, Volume 49, No. 1, Part 2, edited by Mrs. Mildred C. Langner *et alii*; 1961. Washington, D.C.: National Library of Medicine. 10" x 7", pp. 106 with figures. Price not stated.

"Prescription Proprietaries Guide for Doctors and Chemists", edited by Geoff. K. Treleaven, Ph.C., F.P.S.; First Supplement, 1961. Melbourne: Australasian Pharmaceutical Publishing Company Ltd. 8¼" x 5¼", pp. 70. Price not stated.

The Medical Journal of Australia

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NOTIFICATION OF DISEASE.

THE notification of disease to health authorities has been an accepted practice since the latter part of the last century. Traditionally it has been for the purpose of arranging routine disinfection and measures of isolation deemed necessary for the prevention of spread of infection. Today, however, the position has changed somewhat. Measures of disinfection and isolation are not now regarded as of value for some of the diseases for which they were formerly applied, and they certainly do not apply to many diseases which now have to be notified. For purposes of notification one must discriminate between infectious diseases and notifiable diseases—a number of notifiable diseases are not communicable.

The purpose of disease notification can be considered at four distinct levels. The first and most important is that of the local health authority, which needs to be informed of outbreaks of disease within its own particular area as well as in the areas from which the disease may enter. The other three levels are those of the State or region, the nation, and, in some cases, the world. The notification of communicable disease serves a number of immediate purposes, the first of which is to secure prompt action to prevent the spread of infection. It is important to ascertain the source of the disease and to inhibit the action of the infecting causes as far as is practicable. It may also be necessary for the health authority to confirm the diagnosis and check the treatment being given, and in some cases contacts will need to be examined, immunized and kept under surveillance. These purposes, it will be appreciated, apply whether infection is from human sources (for example, an undetected case of the same disease or a carrier), or from water or milk infected by discharges from an infected person, or from some other source. The value of the notification will depend in large measure upon the extent to which action for the control of the notified disease is or can be exercised. A further development is the dissemination of epidemic news, warning the health authorities and people in the affected area, as well as those in adjoining areas, and at times those in other countries, of the progress of the outbreak. Medical officers of health in other areas need to know, not only that an outbreak of disease has occurred, but also whether it is an outbreak which has not yet reached their particular areas but is likely to do so, whether it is part of a general outbreak in which their areas are already involved, or whether it indicates an independent spread from a new focus. Notification also provides an opportunity to educate parents, householders, teachers and social workers and, still more, the staff of the local health authority by means of interviews, inspections and investigations.

Special comment may with advantage be made on staphylococcal infection of the new-born and on breast abscess. The primary purpose of notifying these diseases is not to provide a measure of the incidence of these infections, although to the epidemiologist this is an interesting and instructive aspect; the purpose is rather to enable the health authorities to be informed in time of infection appearing in private practice among women and infants discharged from maternity hospitals. Appropriate and prompt preventive action can then be taken to correct nursing or medical procedures in these institutions and to avert epidemics of staphylococcal infection of the new-born there. Without this source of information, the health authority could not identify hospitals in which procedures, either medical or nursing, were dangerously defective until fatalities among the new-born had brought the fact to notice. In addition it needs to be realized that morbidity data provide information unobtainable from mortality data.

Apart from these immediate purposes served by the notification of communicable disease, there are certain subsequent purposes served by the notification of certain non-communicable as well as communicable disease. These purposes are not just academic, but can be of great practical importance to the individual and the community. The basic purpose is to obtain scientific knowledge, especially of the kind that will assist health authorities to plan more effective programmes for the prevention and control of these diseases, whether or not they are communicable. Information is required on the seasonal, annual, epidemic and cyclical prevalence of the disease for use in epidemiological studies on the natural history of disease, on its epidemicity, and on its relation to age and sex, to urban and rural life, to social and environmental conditions, and to the complex meteorological conditions involved in season and climate. It may also be possible to improve diagnostic efficiency in respect of particular diseases where this is an important objective (i) by giving publicity to and bringing to the notice of practitioners the fact that the discovery of the disease is regarded as of social importance, and that the community is especially concerned about it, (ii) in the case of rarer diseases by calling attention to places where cases may be available for observation by practitioners who may wish to extend their experience, and (iii) by indicating, perhaps by a deficiency of notification in relation to deaths, those areas where special steps may be taken to improve diagnostic facilities. Notification will contribute to the study of the time trends of incidence in local areas, in regions and in the country as a whole, thus assisting the evaluation of the effectiveness of immunization programmes or other control measures on an objective basis. It will also contribute to the system of total sickness statistics in the community, illustrating the incidence of disease by age, sex, occupation and other factors, and its social implications. The needs of undergraduate curricula in medical schools will be met, and material will be provided for those engaged in medical research, medical practice and health administration who, from time to time, request

specific data for particular areas of a country or for several countries.

As an example of a non-communicable disease for which notification is of value we may take leukæmia. This is an important condition from the point of view of the public or community health, because it is uniformly fatal, and crude statistics indicate that there has been a considerable increase in incidence over the last 25 years. It is important to know whether this increase is real, what types of leukæmia have been responsible, and the extent of the hazards to which the patients have been exposed. The ultimate objective of such a study is the prevention of the disease, but before this can be pursued the ætiology of the condition must be clarified. It scarcely needs to be said that information is much easier to obtain while the patient is living than retrospectively after death.

The notification of disease can be just another time-consuming chore to the busy practitioner. He is understandably apathetic if he sees in it no practical purpose, but just evidence of a bureaucratic passion for the collection of information which is never used. He is rightly hostile if the only apparent result of the notification is the descent upon his patient's house of local officialdom to perform mystic rites of fumigation and disinfection—rites that are not only anachronistic and useless, but the source of much inconvenience to the household. Fortunately these things are being changed, but the position is by no means as it should be yet. This article has set out, we hope, convincing evidence that the notification of disease can be of the utmost value to the doctor in his daily work and to the community at large, as well as to epidemiologists and research workers. It seems only reasonable to urge that there be full and conscientious cooperation, both from the practitioner in notifying diseases as required, and from the health authorities in making full use of the information so obtained and letting the members of the practising profession see that it is used and is useful.

Current Comment.

CHRONIC PULMONARY TUBERCULOSIS AS A SEQUEL TO PRIMARY TUBERCULOSIS.

For many years the pathogenesis of pulmonary tuberculosis in the adolescent and young adult has been a vexed question. There are two schools of thought; the one maintains that it is due to fresh exogenous infection, the other that it is the result of reactivation of the old foci of the original infection. The question is more than an academic one, as it is fundamental to a public health approach. Adherents of the first school would deem it unnecessary to supervise the infected child once an inactive stage has been reached. If, however, active disease in young adult life is largely endogenous, continuous supervision of these children will be necessary to discover the disease in its early and most curable stage.

Though present trends indicate that the majority of new cases of pulmonary tuberculosis are found in the older age groups, there are enough young persons being discovered with active disease to cause continuing concern. The "all out drive" to eradicate tuberculosis completely, at least in some countries, demands that no public health facet be overlooked.

For many years physicians in the Chest Clinic of the Children's Medical Service of Bellevue Hospital in New York, led by Dr. Edith Lincoln,[1] have been interested in this problem, and they have now made a retrospective survey of 113 individuals developing chronic pulmonary tuberculosis between 1930 and 1959 who had been observed in their clinic as having had "manifest primary tuberculosis". Briefly, "manifest" implies radiological evidence including calcification. In only seven of these patients, despite careful search, was any evidence found of renewed exposure. The interval between first diagnosis of primary tuberculosis and that of chronic disease varied from less than one year, in five girls (four adolescents and one of seven years), to more than 20 years, being more than five years in two-thirds of the patients. In two-thirds of the patients also, it was discovered by routine X-ray examination, minimal disease being found in 75%. A startling side-observation was that of 32 deaths in this series, 22 occurred in these minimal-stage patients. This catastrophe is of course historical, as antimicrobial therapy was then unavailable.

Other interesting facts were elicited. Although ward admissions were evenly divided between boys and girls, only half as many males as females later developed chronic pulmonary tuberculosis. The risk was greater when primary tuberculosis developed at the age of seven or more, but it was greatest in adolescence irrespective of the age at which primary disease occurred. In 40% of cases the condition developed within two years of the menarche. Another interesting follow-up study showed that "of 622 consecutively seen children with uncalcified primary tuberculosis, 35 (7·6%) of the survivors developed chronic disease". It must be noted, however, that the patients came almost entirely from a very low economic level.

This study, then, favours exacerbation of old disease rather than superinfection as the source of chronic pulmonary tuberculosis in young people, and emphasizes the importance of keeping children with primary tuberculosis under prolonged observation. In a country such as Australia, "primary tuberculosis" could well include all children found to react to a tuberculin skin test. Indeed it is becoming evident that *qua* tuberculosis, they are the only group worth following by regular X-ray survey. A logical deduction from this could be that only tuberculin-positive adults should have X-ray examinations of their chests—that is, if the goal is the discovery and elimination of tuberculosis.

A STUDY OF HOME ACCIDENTS.

Dr. I. A. G. Macqueen, Medical Officer of Health in the City of Aberdeen, has carried out a comprehensive study of home accidents in the city of Aberdeen during a two-year period, 1955-1957.[2] Prior to the commencement of this study, the Aberdeen Health and Welfare Department had commenced a Home Safety Campaign for prevention of home accidents. This campaign was conducted largely by personal home visiting and education of parents, expectant mothers and old people in clubs. It was continued during the two-year period of study.

Dr. Macqueen's findings indirectly reveal the success of this preventive campaign, and show, as others have shown previously, that many home accidents are preventable. For example, the hospital rate of admission in Aberdeen for domestic accidents was as low as 0·8 per thousand people per year, which is very considerably less than figures collected from other large cities (two to three thousand persons per year). Another significant finding was the almost complete absence of accidents, other than falls, among old people, a group particularly susceptible to domestic accidents. The survey also shows

[1] *Dis. Chest*, 1960, 38: 473 (November).

[2] "A Study of Home Accidents in Aberdeen: An Investigation Financed by the Nuffield Provincial Hospitals Trust", by Ian A. G. Macqueen, M.A., M.D., D.P.H., F.R.S.H.; 1960. Edinburgh and London: E. & S. Livingstone Ltd. 8¼" x 5¼", pp. 108. Price: 12s. 6d. net (English).

that the age distribution of accidents was unlike that of any other recorded study. One-quarter of all accident victims were under the age of three years, and half were under the age of nine years. In other words, half of all accidents occurred in the one-sixth of the population which was least capable of understanding and acting on reason.

Other significant findings from the survey were that certain types of accidents occurred mostly in certain age groups. Falls were commonest in pre-school children and the elderly, while cuts, burns and scalds were greatest in pre-school children and steadily diminished during life. Accidental ingestion of poison was almost limited to persons under the age of 10 years, and was especially high between the ages of one and four years. Again, certain groups of the community had a much greater accident rate than others; for example, there was a direct and highly significant association between the number of accidents in children in various social grades. There were many fewer accidents in social grades I and II as contrasted with grades IV and V. Certain families and individuals were clearly shown to be accident-prone. Finally, overcrowded homes, poor kitchen facilities and poor lighting were all shown to be of importance in some cases.

Dr. Macqueen clearly considers that there is good evidence to show that many accidents are preventable, and the best means of prevention is by personal education in accident prevention. He recommends that special consideration in education should be given to groups in the community who have a special risk or are more prone to accidents. These comprise the elderly, the isolated person who is often partially cut off from society, the pre-school child, the young school child, and poorer socio-economic groups.

Dr. Macqueen's study can be commended to the attention of all interested in domestic accidents and their prevention.

A PNEUMOCONIOSIS CONFERENCE.

A PNEUMOCONIOSIS CONFERENCE[1] was held at the University of Witwatersrand in Johannesburg, South Africa, in 1959.

The purposes of this conference, which was convened by the South African Council for Scientific and Industrial Research at the request of the South African Government, were to review recent knowledge of all the scientific disciplines concerned in the study of pneumoconiosis and, more importantly from the South African point of view, to make recommendations for future research to be conducted by the South African Pneumoconiosis Research Unit which might prove to be rewarding. This unit is financed jointly by the Department of Mines and the Transvaal and Orange Free State Chamber of Mines, and it has also received a grant from the South African Mine Workers' Union.

There were 67 invited members of the conference, of whom 17 were from Belgium, Britain, Germany, Italy, Switzerland and the United States of America. With membership including mining engineers, physicists, chemists, pathologists, physiologists, radiologists and statisticians, and with such names as Professor J. Gough, Dr. A. Meiklejohn, Dr. J. C. Gilson, Professor E. J. King, Dr. G. Worth, Professor E. C. Vigliani, Professor P. H. Rossier, Professor A. J. Vorwald, Professor T. F. Hatch and Professor E. P. Pendergrass among the participants, it will be obvious that pneumoconiosis was discussed by world authorities in their subject. The controversial workers' compensation aspects of pneumoconiosis were excluded from the discussions.

The president of the conference was Professor S. F. Oosthuizen, who was chairman of a recent Commission of Enquiry into Pneumoconiosis appointed by the South African Government, and upon whose conclusions recent amendments to the Act dealing with compensation for pneumoconiosis in South Africa were based.

The conference discussed the subject of dust sampling and its control, the use of sampling both for routine observations and for research purposes, the methods by which the various parameters of atmospheric dust can be measured, the sources and methods for lessening exposure to dust, the effects upon experimental animals of different dusts alone, in combination and in association with infection of various kinds, and the relation between lung disease and lung dust analysis.

In discussion of the pathological changes produced by dust inhalation, much time was devoted to the important and more recent studies of the association between dust inhalation and changes in the bronchi, the incidence of chronic bronchitis and emphysema in those exposed to dust at their employment and the effects of pneumoconiosis upon the heart as shown clinically and at post-mortem examination. The radiological diagnosis of early dust effects and the correlation of radiological diagnosis during life with the pathological picture as revealed by post-mortem examination provoked interesting discussions.

As would be expected, the assessment of pulmonary disability provides several papers, and pulmonary function testing was the subject of a panel discussion. C. H. Wyndham and F. Lavenne contribute interesting articles on exercise tolerance and effort tolerance tests.

The results are reported of preliminary work concerned with fundamental aspects of pneumoconiosis research, such as the chemical approach to therapy in the pneumoconioses, the influence of colloidal silicic acid on the in-vitro oxygen consumption of tissues, the activity of respiratory enzyme systems in animals after the experimental inhalation of quartz dust, and the presence of mucopolysaccharides and lipids in the lungs of experimental animals, as well as the results of experimental work on the immunological approach to silicosis. Interesting brief contributions include such infrequently discussed subjects as the advice to be given in early stages of dust disease, the treatment of tuberculosis associated with silicosis and the incidence of coronary disease and hypertension in miners.

Pathological and clinical aspects of asbestosis in South Africa were discussed by Wagner and Sleggs. The high incidence of pleural mesotheliomas on the Cape asbestos fields suggests that a very serious hazard may exist there.

At the conclusion of the Conference, a series of recommendations, listed in the publication, was adopted. These are for further research in the fields of ætiology and pathology, as well as in the fields of physiology, radiology and clinical medicine and in the field of dust and engineering. Dr. Orenstein has successfully overcome the difficult problems in editing the contributions and discussions of a conference of this kind, and the publishers are to be congratulated on the production of the volume so soon after the termination of the conference. The book constitutes a valuable record of present opinions of the effects of dust inhalation and of the ideas of experts for future pneumoconiosis research, in both its preventive and its clinical aspects. It will be a standard reference book on this subject for many years.

[1] "Proceedings of the Pneumoconiosis Conference: held at the University of Witwatersrand, Johannesburg, 1959", edited by A. J. Orenstein, M.D., D.Sc., LL.D., F.R.C.P.; 1960. London: J. and A. Churchill Ltd. 9¼" × 6", pp. 678, with many illustrations. Price: 120s.

THE DANGER OF THIN PLASTIC BAGS.

WE welcome the decision of The Plastic Institute of Australia to conduct a publicity campaign, warning the public of the danger of thin plastic bags to young children. This is being undertaken because of the decision to manufacture ultra-thin plastic bags in Australia, such bags having been hitherto only imported. The danger of suffocation if thin plastic is applied to the face, and especially if the bag is drawn over the head, has already received considerable publicity, but repeated warnings are urgently needed to impress on the public the danger of these articles as playthings.

Abstracts from Medical Literature.

ORTHOPÆDIC SURGERY.

Spondylosis of Cervical Part of the Spine.

P. TENG (*J. Bone Jt Surg.*, April, 1960) discusses the mechanisms producing disturbance of the spinal cord and nerve roots in spondylosis of the cervical part of the spine, as illustrated by the findings demonstrated in the operative treatment of 20 patients. The author refers to the few contributions on the surgical management of the condition. He notes that conservative treatment takes pride of place in the literature. In most of his cases in which surgery was required there was a traumatic background. The symptoms in all these cases were progressive and present for at least 12 months. These consisted of the following: pain in the head behind the ears, in the neck, and behind and between the shoulders; dysæsthesia in the involved arm, hand and fingers; involvement of the cord, with thoracic, perineal, bladder and lower limb symptoms and signs. Wasting, weakness, spasticity and, less commonly, loss of sensation occurred; upper motor neuron type of involvement was found in the upper limbs and lower motor type in the lower limbs; disturbance of reflexes was commonly demonstrated. The author notes that the pattern of signs and the symptoms did not always follow a logical sequence. He explains this by supposing partial involvement of individual nerve roots. Such manifestations were hyperactivity of reflexes associated with weakness and wasting of muscle groups. Operation consisted of wide exposure and laminectomy, up to three arches being removed, foraminotomy, excision of arachnoid membrane, bilateral resection of dentate ligaments, partial removal of osteophytic ridges and incision of dural sheath to allow nerve root decompression. Quadriplegia is mentioned as a frequent complication.

Anterior Fusion of the Cervical Part of the Spine.

R. W. BAILEY AND C. E. BODGLEY (*J. Bone Jt Surg.*, June, 1960) discuss the indications and technique of the anterior cervical fusion of the cervical part of the spine. This approach to the anterior surface of the cervical bodies was first described in 1952. The authors note that their experience since 1928 confirms reports that many fractures of the pedicle or articular processes do not heal well, and result in an acute or a slowly developing recurrence of dislocation of the neck, occasionally with drastic neurological consequences. Therefore, they consider that fusion of the involved vertebræ is necessary. This should be performed from behind if there is persistent dislocation of the cervical vertebræ or other evidence of locked articular facets. However, in certain circumstances anterior fusion is more acceptable. This is the case after extensive laminectomy, or when a later laminectomy may be required. When there are associated facio-maxillary injuries the anterior approach is safer for the anæsthetized patient. If there has been any quadriplegia, the anterior approach is less likely to produce further damage. The authors describe their technique fully. They use a morticed inlay graft with cancellous bone from the ileum.

Management of Multiple Injuries.

J. M. C. GIBSON (*J. Bone Jt Surg.*, August, 1960) writes of the results in 59 patients with fracture of the shaft of the femur and a head injury admitted to the Oxford Accident Service between 1949 and 1956. During the same period 4000 head injuries and 263 fractures of the shaft of the femur were treated. He emphasizes the difficulty of treatment, the order of precedence in treatment, and the necessity for compromise in cases of multiple injuries. He notes that it is important that one person should be in charge of the patient under the supervision of the neurosurgeon and the orthopædic surgeon. He notes, too, that this type of case is best treated in an accident service working within a general hospital. Within the Oxford Accident Service immediate treatment consists of maintenance of a good airway, then assessment of the degree of shock and institution of appropriate resuscitation measures, after which a general and a neurological examination are carried out. The last is essential to assess the progress of any intracranial disturbance. Pulse rate, blood pressure, respiration rate, temperature and the state of the pupils are recorded on arrival and at half-hourly intervals. It was found that a Thomas splint was usually the best means of immobilization of the fractured femur. Usually up to eight hours' observation was sufficient to give a clue to the progress of the head injury. The patient then showed signs of either improvement or deterioration. In cases in which improvement occurred, it was then possible to use a short anæsthesia to close open wounds and to manipulate the fracture and fit definitive splinting. The use of open methods such as the insertion of a Küntscher nail usually involved an unjustifiable risk, even though nursing might be made easier. On occasions, when the patient was very restless, a plaster spica was used. This allowed the patient to be suspended and moved about should the state of consciousness deteriorate. However, the patient could be turned in a Thomas splint attached by fixed traction. If the patient's condition did not allow general anæsthesia, skeletal traction could be used. The pin was inserted through the tibial tubercle under local anæsthesia. Definitive treatment of the fracture could be carried out after an interval of several days, or even much later. The presence of an open fracture might necessitate an earlier anæsthetic. This might delay cerebral recovery, but could be justified if anoxia was carefully avoided and minimum time was taken to close the skin after *débridement*.

Flexion Contracture of the Knee.

E. W. SOMMERVILLE (*J. Bone Jt Surg.*, November, 1960) discusses the types of flexion contracture of the knee. The first type is simple and after release of tight structures by division or stretching the knee comes into full extension. The second type will not come into full extension unless the upper end of the tibia displaces backward. The author considers that this happens because of a tight, thick anterior cruciate ligament. He describes the surgical approach to division of the ligament, and notes that it may be difficult to find in the joint. He considers that it becomes shortened because it is relaxed when the knee is flexed. This is illustrated with diagrams.

Conservative Treatment of Congenital Dislocation of the Hip.

J. WILKINSON AND C. CARTER (*J. Bone Jt Surg.*, November, 1960), review 200 patients with congenital dislocation of the hip. They emphasize the case for conservative management and define the indications for surgery. In their search for a prognostic sign, they examined the degree of slope of the acetabulum of the undislocated hip. Undislocated hips were classified according to this measurement as "normal", "moderately shallow" and "shallow". The authors show that in unilateral congenital dislocation of the hip the relationship between the result of treatment and the angle on the opposite unaffected hip is very close and statistically significant. The authors believe that the development of the unaffected hip gives an accurate estimation of the potential development of the dislocated hip. Conservative treatment is therefore the treatment of choice in unilateral congenital dislocation of the hip with a "normal" unaffected acetabulum; in such cases operation would be indicated if the reduction is eccentric and persists for more than two or three months, or in the few cases in which the dislocation is not reduced after six weeks' traction. Early operation is indicated in unilateral cases in which the opposite hip joint is "shallow" and probably also if the opposite hip joint is "moderately shallow". The authors note that the acetabular index is not helpful in bilateral congenital dislocation of the hip. Early operation is therefore indicated, as the results of conservative treatment are worse than for unilateral cases as a whole. The authors consider that anteversion is an exceptional cause of failure. In the later cases of the series all reductions were achieved by traction and gradual abduction of both legs. After reduction, both legs were held in abduction and neutral rotation either in a plaster cast or in Dennis Browne harness.

Congenital Dislocation of the Hip.

I. G. MACKENZIE *et alii* (*J. Bone Jt Surg.*, November, 1960) summarize their policy of management of congenital dislocation of the hip. Conservative treatment, namely abduction on a frame and reduction by cross pull of no more than three pounds, is discussed. The frog position is considered to predispose to avascular necrosis. The authors manipulate to achieve reduction in children under six months. If the hip is reduced on the frame, the child is put in a Batchelor plaster cast for a period of up to 10 months. Stiffness occurred in one hip from prolonged immobilization. Stiffness is usually the result of avascular necrosis. The authors stress the importance

of early diagnosis, and distinguished subluxation from dislocations. They are no longer enthusiastic about arthrography. Statistically, anteversion is found to be unimportant. After reduction, the need for osteotomy was obvious when it was necessary. Frontal inclination of the socket is discussed, and the need to correct excess valgus deformity in certain instances. The indications for surgery are dealt with in detail, and the various surgical procedures discussed. No child was kept on a frame in an effort to obtain reduction for longer than one month, or for more than three months in a Batchelor plaster cast if reduction was incomplete; open reduction was performed if the hip remained "standing out" after this period. The authors stress that the limbus is really the least important of the various obstructions. The crucial problem of the potential development of the acetabulum is tackled by preventive acetabuloplasty in children aged less than three years. This is a type of shelf operation. The authors note that it can be performed later with satisfactory results. The Colanna operation was also used in later cases. The authors consider that the debate as to the best method of treating congenital dislocation of the hip will go on for years.

PÆDIATRICS.

Viral Infection as a Possible Cause of Sudden, Unexpected Death in Infants.

E. GOLD *et alii* (*New Engl. J. Med.*, January 12, 1961) point out that studies have indicated that from 25% to 44% of all infants who die after the neonatal period but before the age of two years do so suddenly and unexpectedly without post-mortem findings adequate to account for death. The authors attempted to isolate viral agents from tissues obtained at autopsy from 48 infants whose deaths were sudden and unexpected and from 2 who met traumatic deaths. Viral agents were detected in specimens obtained from 12 subjects. In 5 the agent was isolated from stool or pharynx, and in 7 from central nervous system tissues. All agents were members of the enterovirus family, Group A Cocksackie viruses predominating. No agents were isolated from the two infants who died of trauma. These results do not demonstrate that viral infection is the cause of sudden, unexpected death, but do suggest a relation between viral infection and sudden death in infants. If infection should prove to be important as a cause, it seems likely that no single agent would be implicated.

Obstructive Urinary Anomalies in Children.

J. MCGOVERN (*Pediatrics*, January, 1961) states that inadequate emptying of the urinary tract, in effect obstruction, underlies the overwhelming majority of urinary infections in infancy and childhood. This is certainly true concerning persistent or recurrent infections, and the suspicion is great that the same holds even for apparently non-recurrent idiopathic infections. Such infections are being increasingly recognized as essentially persistent conditions endangering the kidneys, rather than self-limited, transient, simple invasions. A retrospective study of the hospital records of 265 cases of obstructive uropathy in children demonstrated that only 19 patients had no urinary signs or symptoms. In 30% of cases the first clear indication of an obstructive anomaly was fever, and in another 35% recognizable urinary difficulties elicited solely from the history were the first indications. Abdominal pain, gastro-intestinal complaints and failure to thrive were common. Pyuria was present in at least 70% of cases. While most obstructions are readily detectable by urological means, catheterization and intravenous pyelography particularly, there are poorly understood uropathies which are difficult to recognize. Although antibacterial medication will often suppress the invading organism, a true cure rarely results until the obstruction is relieved. It is important to remember that the kidneys can be destroyed by obstruction alone, in the absence of or during the suppression of infection.

Anaphylactoid Purpura.

R. VERNIER *et alii* (*Pediatrics*, February, 1961) studied 45 children with anaphylactoid purpura. Evidence of recent streptococcal infection, as determined by positive ASO titres, was found in 13 out of 39 patients, an incidence of positive ASO titres only slightly higher than that expected in children with non-streptococcal illness. This observation suggests that streptococcal infection is not the major cause of anaphylactoid purpura. Microscopic study of skin biopsy specimens from 12 children showed perivascular cellular infiltration of the dermis. Numerous leucocyte-platelet thrombi were observed in small dermal vessels. Muscle biopsy specimens usually appeared normal. Kidney biopsy specimens from 11 children with anaphylactoid purpura-nephritis of variable severity and duration were studied. The principal microscopic abnormality consisted of focal lesions of fibrinoid deposition and endothelial proliferation within scattered glomeruli. Renal biopsy specimens obtained during clinical recovery from anaphylactoid purpura-nephritis showed focal glomerular scars. The authors review clinical, experimental and pathological data which support the concept that anaphylactoid purpura is a form of diffuse vascular disease, probably caused by hypersensitivity to a variety of agents.

Post-Injection Sciatic Nerve Palsies.

F. GILLES AND J. FRENCH (*J. Pediat.*, February, 1961) review 21 cases of sciatic palsy, associated with intragluteal injections, in pædiatric patients. Eighteen patients were followed up over periods ranging up to three years. Six of these recovered completely within periods ranging from 24 hours to 13 months. Four showed no improvement after intervals ranging between 7 and 36 months. The remainder showed partial recovery. Direct injection of neurotoxic material into or near the nerve is, in the authors' opinion, the most probable mechanism of sciatic nerve damage. In the neonate, infant or debilitated pædiatric patient it is extremely easy to inject into or near the sciatic nerve. On the basis of anatomical, experimental, pathological and clinical observations, the authors suggest that the buttock be abandoned as a site of injection in infants and children, the lateral distal third of the thigh being recommended as a preferable injection site.

M. A. COMBES *et alii* (*J. Amer. med. Ass.*, July 23, 1960) state that injection injury of the sciatic nerve is more common than is supposed, and can result from injections of commonly used antibiotics and other agents into the buttocks, especially in young infants. Twelve cases are reported; in most of these a paralytic drop foot resulting from nerve injury had been misdiagnosed as a congenital lesion or the result of unrecognized poliomyelitis. The authors state that demonstration of sensory loss and the absence of sweating over the distribution of the sciatic nerve branches are the most valuable clues to the diagnosis. Surgical exploration of the buttock in the three most recent cases revealed marked scarring in and about the sciatic nerve. Recovery has been poor. The authors conclude that the mid-anterior part of the thigh is the preferred site for all intramuscular injections in infants and young children.

Bulging Fontanelle due to Tetracycline Therapy in Infants.

J. FIELDS (*J. Pediat.*, January, 1961) states that the most frequent untoward side-effect of therapy with tetracyclines is gastro-enteritis, but that benign intracranial hypertension manifested in infants by bulging of the fontanelle occurs occasionally. The relationship between tetracycline therapy and increased intracranial pressure seems to be more than coincidental. Withdrawal of the drug was associated with prompt return of the fontanelle to normal in the two patients reported in detail by the author. They were not receiving any other medication, and subdural hæmatoma and meningitis, the more common causes of bulging fontanelle, were not present in either patient. The mechanism of this reaction is not clear. No relationship was observed between the dose or length of therapy and the production of the bulging fontanelle.

Duodenal Ulcer in Childhood.

W. MICHENER *et alii* (*Amer. J. Dis. Child.*, December, 1960) reports that between the years 1930 and 1958 duodenal ulcer was diagnosed in 109 infants and children at the Mayo Clinic. Later information concerning 92 of them was obtained. Fifty-three had no further difficulty after treatment of the initial episode, but 39 had persistent or recurring symptoms. Forty-four of the 92 patients were 15 to 37 years old at the time of follow up. Twenty-two of this group still had ulcer symptoms and 22 had been asymptomatic since the initial episode. There thus appears to be a 50% chance that a duodenal ulcer which begins in childhood will cause symptoms when the patient is an adolescent or adult.

Medical Societies.

PÆDIATRIC SOCIETY OF VICTORIA.

A MEETING of the Pædiatric Society of Victoria was held at the Royal Children's Hospital, Melbourne, on June 8, 1960.

An Unusual Corrosive Burn of the Pharynx.

MR. A. WAKEFIELD presented the clinical history of a boy, aged six years, who had been referred to him by Mr. C. F. H. Pyman in September, 1958. Mr. Wakefield said that the boy had been well until he had swallowed some caustic soda two years previously. It was perhaps worth noting that his father was an industrial chemist; such things obviously happened even in families who were well informed. Apparently that episode had been regarded as a rather minor one, not necessitating the child's admission to hospital. However, some months later it was noticed by his parents that his voice had changed appreciably, that he was getting more frequent colds, coughs and sore throats than previously, that he had developed a chronically running nose and that he was rather slower to eat his food than previously. He had attended the hospital with those symptoms and had been referred to Mr. Pyman's ear, nose and throat clinic, where it was considered that his tonsils and adenoids should be removed.

In May, 1958, he had therefore been admitted to hospital and that operation carried out. However, at the time of operation, it was observed that he had a webbing of the pharynx just above the epiglottis and entrance to the œsophagus with an opening three-eighths of an inch in diameter. Nothing had been done about it until he was readmitted to hospital in June, 1958, when the web stricture of the pharynx was divided with a cautery. Œsophagoscopy at that time showed a small scar at the level of the crico-pharyngeus without stricture in the œsophagus. He was discharged from hospital three days later, able to eat soft foods, and his condition appeared to be satisfactory at that time.

One month later he was again beginning to have difficulty in swallowing, his voice had grossly changed and become hoarse and he had been losing some weight. He was readmitted to hospital two weeks after that, when further cauterization and dilatation were carried out, after which an attempt was made over the next two weeks to maintain the passage by the daily insertion of bougies. There had been considerable difficulty in passing them, and from time to time considerable doubt as to whether they were in fact passing the stricture. On September 4 pharyngoscopy revealed that the stricture was tighter and more rigid than ever, and the child was referred to Mr. Wakefield for further management.

Mr. Wakefield said that he had examined the pharynx a day or two later, and found that at that time the opening in the lower part of the pharynx through which the patient had to breathe and take his food was considerably less than one-quarter of an inch in diameter. He was breathing noisily and hoarsely, and it was difficult to get anything other than a completely fluid diet into him—and that only slowly, because of associated respiratory difficulty. It was apparent that an acute obstruction from secretions or from food particles might occur at any moment, and some type of definitive repair of the pharynx was thought to be necessary at an early date. By that time the stricture had become very tight, rigid and inflamed, and it was apparent that a substantial amount of the mucous membrane of the pharyngeal lining had been lost. The problem was different substantially from the usual corrosive strictures of the œsophagus at a lower level, in that this was one which affected the respiratory as much as the alimentary passage, and indeed, as was subsequently shown at operation, it affected the pharynx right at the point of division into alimentary and respiratory pathways. It was also shown subsequently by open operation that the greater part of the epiglottis was missing, only a small stub being left, and it was surprising that there had not been a great deal more embarrassment to the child than there had been over the previous two years.

Mr. Wakefield went on to say that there were two, and only two, means of replacing lining tissue in such an area, one being by free graft and the other by pedicle flap. Transfer of mucous membrane by either means was difficult, and a source of material was not readily available for large areas. However, it had been found that skin behaved in a satisfactory manner in that area and was a suitable material for replacement. In general, free grafts for such problems were a great deal more satisfactory than the more bulky pedicle flaps. They could be so cut as to have no hair follicles, and they could be introduced in a way that did not leave bulky redundant tissue in the region. However, to ensure the take of a free graft in such an area was a very difficult technical matter. After careful consideration, he had thought that he should make an effort in the first instance to deal with the problem by free grafting, and a prosthesis was constructed which was attached by a long arm to a splint on the upper teeth. The scarred area of the pharyngeal wall was incised, the lining being allowed to retract into its normal position and leaving a very large, almost circumferential defect. A mould draped with split skin graft was attached to the prefabricated prosthesis and a tracheostomy was established. It was thought that intravenous feeding would suffice for the few days necessary to ensure the take of the graft.

Mr. Wakefield said that in the immediate post-operative period, too enthusiastic suction on the part of the nursing staff had the effect of sucking the graft off the mould, and he was called back the same evening to insert a new graft. The management of the child in the next few days was extraordinarily difficult despite heavy sedation, and it was found quite impossible to control the movements in that region involved in normal reflex swallowing actions and movements of the head and neck; and he had considered that it would be a very lucky event if very much of the graft survived. In the upper part of the pharynx such procedures were very satisfactory, because the area of the naso-pharynx moved with the maxilla to which the splint was attached and there was little or no independent movement, but the only form of adequate fixation was to the maxilla, and, of course, in the lower part of the pharynx a great deal of movement occurred independently of the maxilla. Splintage to the lower jaw was unsatisfactory because of movement of that structure, and he had been unable to devise any other means of more adequate fixation in the case under discussion.

At the first dressing a few days later, it was found that a reasonable part of the graft had survived, and he thought that at least it would tide over the then more or less emergency period and allow a considerably bigger opening for swallowing and breathing. However, it had not been a sufficiently good take to regard as a permanent solution to the problem. The tracheostomy tube was removed a fortnight after the operation, and the child was at that stage breathing and swallowing satisfactorily, although he still had some raw areas on the pharyngeal wall where parts of the graft had missed, and where subsequent scarring could be expected to contract and reproduce the stricture to some degree.

On November 3, 1958, the child had been readmitted to hospital for examination. He was well, but he still had some disturbance of his speech and some wheezing at night, and although taking food well, he was slow, and could not manage anything that was not finely broken up. Mr. Wakefield had considered at that stage that the difficulties associated with free grafting were such that it would be best not to persevere with that method, and on November 10 an extensive procedure had been carried out. On the right side of the neck a lateral pharyngotomy was carried out through the bed of the greater wing of the hyoid bone, which was excised. That fortunately immediately gave access to the stricture, and the exposure was most satisfactory. The scar was again excised, thus reestablishing the defect, and a long pedicle flap was raised vertically on the right side of the neck based upwards and transposed in through the pharyngotomy to line the defect. The defect at the site of origin of the flap on the neck was closed directly. The flap was so designed as to use the skin from the lower half of the neck in order to obviate as far as possible the problems of hair growth in later life. The tracheostomy was reestablished. For the first few days only intravenous feeding was used, but as soon as the immediate post-operative condition had settled down a few days later, oral feeding was commenced, with a minimum of leakage from the neck stoma. On December 1, the second stage of the procedure was carried out. The flap was divided at its base, and as much as necessary was set in to provide an adequate pharyngeal aperture. The neck was then closed in layers, with direct suture of the remaining skin defect. The tracheostomy was allowed to close a week later, at which time the child's respiration was adequate, and he was taking a soft fluid diet satisfactorily.

Mr. Wakefield said that the execution of the procedure presented no particular problems throughout, and was in direct contrast to the difficulties associated with the attempt

at free grafting. Inspection of the area a month later under general anæsthesia showed the flap to be well settled in, and although it was a little bulky and protruded into the pharynx more than was desirable, it had nevertheless allowed a large passage through the pharynx with no evidence of clinical stenosis. The child had been examined since then at regular intervals of three months in the out-patient department, and had put on weight and looked well. He was eating a satisfactory diet, although his mother said he took his time over it, and his airway was adequate, although she said that he snored a little at night and was a rather more noisy sleeper than normal.

Mr. Wakefield then discussed the points that came out of the history from a practical point of view. The first was that a stricture of the pharynx of such a degree could exist for two years without causing more than casual symptoms, despite what must have been an ever-present risk of acute obstruction from blockage by food particles. The second was the curious fact that one major stricture of that sort had been the only effect of the swallowing of the corrosive, without any evidence of undue scarring or stricture anywhere else along the œsophagus and pharynx. The third was the special problem that existed when the stricture was at that level, and when the effect was on both the alimentary and respiratory tracts. The fourth was the necessity to recognize that if tissue was lost, then the optimum means of dealing with the resultant stricture was by replacing the amount of tissue that had been lost. Mr. Wakefield held that the division of what had been thought to be a simple soft-tissue web across the pharynx by means of a cautery, and then subsequent attempts at maintenance of the pharynx by dilatation, had aggravated the condition rather than relieved it. At the time when Mr. Pyman had first shown him the patient and suggested that the management should be along those lines, he himself had thought that if the constricting web was simply a thin membrane then the simple procedure might improve the state of affairs, and he had agreed to it as a first step. In retrospect he thought that that had been a wrong assessment of the situation, and that the area of scarring had been far more extensive than appeared from a view from above. He considered that possibly an extensive X-plasty on the existing web would have been a better procedure, and might have obviated the necessity for the more elaborate grafts that had been later necessary. The fifth point was the extraordinary difficulty of applying and maintaining free grafts in that situation. That was in direct contrast to the upper naso-pharyngeal area, where the insertion of free grafts, although technically difficult, could be satisfactory, and the maintenance was nowhere near the same problem. Naso-pharyngeal stenosis was always best treated by free grafts on moulds and fixed to the upper dentition, rather than by the more cumbersome method of the use of flaps. The sixth point was that the bulk of tissue involved in the transfer of pedicle flaps for that purpose was a decided disadvantage, and although there was an adequate passage, the protrusion of the bulk of the flap into the pharyngeal cavity still made for some noisy breathing, and affected the patients' speech to some degree. Finally, the problem of potential hair growth on that cervical skin in later life was another disadvantage of that particular method of repair. Fortunately, the child was of the type not likely to have excessive hair growth, and he had selected the lower part of the neck, which was normally fairly sparse in hair growth, for the purpose. Despite the difficulties, he did not think that the patient was likely to have any major problem of an obstructive nature in the future. Mr. Wakefield had not seen a similar problem at that level previously, and thought it sufficiently interesting to be worth recording.

Primary Tuberculosis following Circumcision.

DR. H. N. B. WETTENHALL presented the case of a boy, one of identical twins, who developed primary tuberculosis of the penis after circumcision. The history was that three weeks after he had been circumcised, a small ulcer appeared in the region of the corona and failed to heal. In association with the ulcer, the glands in the left inguinal region increased in size, and when the child was examined six weeks after circumcision, they had commenced to soften in the centre. The Mantoux test (1:1000) produced a positive result, and pus aspirated from the inguinal glands yielded *Mycobacterium tuberculosis*. The glands were then excised, and the boy was treated with a course of streptomycin, isoniazid and paraaminosalicylic acid. The penile ulcer healed within two weeks, but about three weeks after the commencement of chemotherapy the glands in the right groin increased in size and became fluctuant. They were excised in similar fashion to those on the left, and tubercle bacilli were again found to be present. Since that operation the boy had thrived and progressed normally. It had not been possible to determine the source of the primary infection.

The H. D. Stephens Memorial Meeting of the Pædiatric Society of Victoria was held at the Royal Children's Hospital, Melbourne, on July 13, 1960.

The Disordered Physiology of Ventricular Septal Defect.

DR. A. VENABLES, discussing ventricular septal defect, said that the common form was that just inside the tricuspid valve in the inflow portion of the right ventricle. Physiologically the atrial septal defect and ventricular septal defect differed, in that the interatrial shunt occurred essentially in ventricular diastole while the interventricular shunt was systolic. The magnitude of the shunt in both cases was determined ultimately by two factors, the size of the defect and the pulmonary vascular resistance.

In the normal circulation, once flows had become equalized after duct closure in infancy, the mean pressures in pulmonary and systemic circuits reflected the resistance to flow in those areas. Pulmonary systolic pressure (30 mm. of mercury upper level) was normally much less than the corresponding systemic pressure (120 to 150 mm. of mercury in adults). Mean pressures had a rather similar relationship. The normal pulmonary vascular resistance was therefore approximately one-sixth of the systemic resistance. Resistances could be calculated, provided that one knew the mean pressure gradient and the actual flow. They could be measured as degrees/second/cm.$^{-5}$, or as the larger Wood units, obtained by dividing pressure as millimetres of mercury by flow in litres per minute without regard for unit detail. (One Wood unit equalled 80°/second/cm.$^{-5}$.)

When a ventricular septal defect existed with a normal resistance ratio, flow would be from left ventricle to right ventricle and would depend on the size of the defect. A small ventricular septal defect might produce a shunt undetectable except by certain special investigations, yet with a characteristic pansystolic murmur. With a large ventricular septal defect and normal pulmonary vascular resistance, pulmonary flow might be very great, perhaps three times normal. The pulmonary artery pressure might rise as a result of such flow, as pressure was proportional to flow and resistance. The common misuse of the term "pulmonary hypertension" was worthy of comment. That meant nothing more or less than raised pulmonary artery pressure. It did not indicate whether that increase in pressure was due to flow, or to increased resistance, or to a combination of both.

Pulmonary vascular obstruction occurred in a variety of circumstances, but was quite common in ventricular septal defect. In fact, ventricular septal defect with large flow and normal resistance was fairly uncommon. In the fœtus, the mechanical condition of the pulmonary capillaries gave great resistance to flow, which decreased considerably with gaseous pulmonary ventilation. Subsequently resistance might rise, as a result of organic occlusive changes with medial hypertrophy and intimal proliferation, and at times of clotting, in small arteries and arterioles. As far as intracardiac defects were concerned, the two definable mechanisms which seemed to potentiate those changes were increased flow (with probably some relation to pressure) as in ventricular septal defect, and pulmonary venous obstruction as in mitral stenosis. In addition, there was a third factor of possibly genetically determined changes which resembled idiopathic pulmonary hypertension, with early development of occlusive disorder and high resistance, in association with, but apparently independent of, the defect.

Oxygen tensions were of relevance to that subject. Anoxia could cause elevation of the resistance, as in the neonate breathing low tensions of oxygen, and an increased oxygen supply could decrease it, with diminution, for instance, of right-to-left shunting in balanced defects by breathing pure oxygen.

In ventricular septal defects, it was generally believed that resistance had a tendency to increase progressively, although that was not fully documented. The rate of increase was unpredictable, but probably varied greatly and was often slow. Occurrence of such an increase in atrial septal defect had been documented by Lewis Dexter. There the rise was usually a gradual one.

There was a spectrum of ventricular septal defect and pulmonary vascular resistance. At one end of the spectrum was the ventricular septal defect with normal pulmonary resistance and high flow. In that case there was a large

shunt through the defect, with a loud precordial pansystolic murmur and thrill. The left ventricle, which was coping with the load, was hyperactive, with an easily palpable but localized impulse in the left nipple region. The electrocardiogram confirmed it. Increased flow through the pulmonary artery produced plethora and pulsation. The increased return to the left ventricle via the left atrium and mitral valve produced a characteristic short mid-diastolic mitral flow murmur. Those were the signs of significant uncomplicated ventricular septal defect—the most suitable form for repair. In such cases, preoperative cardiac catheterization probably was not required. With smaller shunts there was no significant left ventricular impulse and no flow murmur, and plethora might be difficult to detect. The pansystolic murmur then became the only sign. In such cases operation was probably not justified except on the grounds of prevention of bacterial endocarditis, as the risks of treatment outweighed those of the disease.

As pulmonary vascular resistance rose, flow towards the right ventricle decreased and the right ventricle pressure rose. The physical signs were correspondingly modified. Defects in which there was a raised pulmonary vascular resistance were generally large, and of a size which led to "governing" of the right ventricular pressure by the systemic pressures (in the left ventricle and aorta) when the pulmonary vascular resistance exceeded the systemic level. Thus pressures in the two ventricles tended to become equilibrated at normal systemic levels and then to remain at those levels with a decreasing left-to-right shunt. Bidirectional shunting occurred at different phases of systole, and finally right-to-left shunt predominated, with obvious cyanosis and digital clubbing. That produced the so-called Eisenmenger complex. Lesser degrees of reversal might be detectable only by arterial oxygen measurements. They might not be a contraindication to surgery provided that the actual pulmonary flow still exceeded normal, so that there was still a continuing stimulus to the development of further occlusive changes. If there was a predominant and substantial left-to-right shunt, even though the pulmonary artery and systemic pressures were balanced with increased pulmonary vascular resistance, there was reason to close the defect with a probability of subsequent improvement, provided the patient survived the greatly increased operative risk. Equilibration of pressures also occurred with very large defects in which there was virtually a single ventricle. In hearts of that type there might be streamline flow without the free mixing one would expect. A similar effect on hæmodynamics was produced by the association with ventricular septal defect of obstruction in the normal right ventricular outflow tract. That obstruction had a similar variation in severity to changes in pulmonary vascular resistance.

There was also a spectrum of right ventricular outflow obstruction and ventricular septal defect. From the uncomplicated ventricular septal defect at one end, one passed to mild obstruction, so called "ventricular septal defect with pulmonary stenosis", in which there was still substantial left-to-right shunt. Somewhat higher degrees of obstruction produced the fairly balanced bidirectional shunts of the so-called "acyanotic Fallot", and severe obstruction produced the predominant right-to-left shunt of the more classical Fallot type. In those cases once again, the ventricular septal defect exerted a "governing" action on the level of right ventricular pressure. No matter how great the right ventricular outflow tract obstruction, the right ventricular pressure did not rise above the left ventricular pressure, except in those unusual cases in which there was some obstruction with the ventricular septal defect itself.

It was important to note that the right-to-left shunt in both types of obstruction — pulmonary stenosis and pulmonary vascular occlusion—was never anywhere near the size of the left-to-right shunt of uncomplicated large ventricular septal defect. The right-to-left shunts occurred at low pressure gradients with equilibrated pressures, and were silent in both groups. The murmur of the Fallot type was of course due to flow through the obstructed outflow tract. In ventricular septal defect with outflow tract obstruction and mixed shunts, the signs would be contributed to both by left-to-right ventricular septal defect flow and by the outflow obstruction.

The concept of aortic overriding, as applied to the Eisenmenger complex and the Fallot abnormality, with both of which it was associated by definition, required some comment. Aortic overriding brought to mind a concept of septal deviation beneath adjacent pulmonary and aortic valve rings. However, the ventricular septal defect was in nearly all cases just inside the tricuspid valve, separated from the pulmonary valve ring by the crista supraventricularis. It was, of course, there in close relation to the aortic valve. In fact, in some cases an aortic cusp prolapsed into the defect, producing the syndrome of ventricular septal defect with severe aortic incompetence and a considerable increase in the left ventricular load. Looking up from the right ventricle through those defects, one could see straight into the aorta. In addition, one could sometimes demonstrate a direct path taken by the cardiac catheter into the aorta. However, the direction of flow depended on the relative outflow resistances.

Right ventricular outflow tract obstruction was usually congenital and essentially fixed. However, in some cases it might develop as the result of work hypertrophy of the right ventricle producing infundibular obstruction by the thickened crista supraventricularis. A similar situation occurred in the right ventricle in some cases of isolated pulmonary valve stenosis, and in the subvalvular region of the left ventricle with systemic hypertension and with aortic valve stenosis. Gasul had shown such an obstruction developing in the right ventricle in infants with large flow ventricular septal defects, with decrease in pulmonary flow and improvement in the baby's condition. Infants with large ventricular septal defects often did very poorly in their first year, but subsequently improved. That was by some attributed to the lag between reversion of the fœtal arteriolar pattern and the acquisition of reactive pulmonary vascular changes.

Dr. Venables said that it should be remembered that gradients of up to 30 to 35 mm. of mercury occurred across normal outflow tracts (usually at valve level) in the presence of large flows. In such cases the pulmonary artery pressure, not the right ventricular pressure, was the significant one in relation to the determination of the pulmonary vascular resistance.

In general terms, the severity of the right ventricular outflow tract obstruction reflected the degree of distortion of that area and the probable surgical difficulties. However, that was not a fixed rule, and one sometimes met localized severe obstructions in the valve or infundibulum which could be dealt with more easily. Selective angiography would help to define the outflow tract before operation. In cases of right ventricular outflow tract obstruction, surgical repair demanded relief of the tract obstruction as far as possible, and closure of the ventricular septal defect. That group of patients often required help because of anoxia rather than the mechanical cardiac load. The latter was not great, because of the "governing" effect of the ventricular septal defect with the limitation of right ventricular pressures to systemic level, despite the magnitude of the outflow tract resistance.

In summary, the uncomplicated ventricular septal defect with a large shunt had characteristic signs related to left ventricular overload and to the shunt itself. The two common complications of ventricular septal defect were elevation of pulmonary vascular resistance and right ventricular outflow tract obstruction. In both cases there was a similar spectrum of disordered physiology dependent on the varying severity of the pathological obstructive changes in the lung vessels and the outflow tract respectively. In both, the ventricular septal defect ordinarily provided a governing effect holding right ventricular pressures at systemic levels, thus limiting systolic or pressure loads. In both, the ventricular septal defect was usually in close relation to the aortic root, but the direction of flow across the defect was essentially determined by the relative difficulties of escape of blood into the peripheral circuits—in other words, by the ratio of the pulmonary and systemic vascular resistances. The patient with high pulmonary vascular resistance had an inoperable condition, while the patient with an extremely obstructed outflow tract usually presented a very great technical problem. In both situations there was a spectrum of disorder within which certain syndromes had in the past been defined as entities. Understanding of the basic disorders and their spectra as outlined rendered the continued recognition of such syndromes undesirable except as convenient shorthand labels indicating rough grades of severity.

The Heart-Lung Machine.

DR. M. CASS discussed the heart-lung machine. He said that defects within the heart could be corrected most satisfactorily if it was possible to gain access to the inside of the heart. At first sight that seemed a relatively simple procedure. The heart was a pump, and it should be easy to construct a mechanical pump to take over the heart action for an hour or so. Unfortunately the problem was not quite so simple in practice.

To by-pass the heart, the blood was drained from the venæ cavæ before it reached the right side of the heart That was done by cannulating both venæ cavæ and leading the blood off to a pump to pump it through the lungs. The lungs were perfused by cannulating the pulmonary artery near the pulmonary valve proximal to the bifurcation of the pulmonary artery, or by passing the cannula through the right ventricular outflow tract and into the pulmonary artery via the pulmonary valve. Both methods of cannulation for the perfusion of the blood through the lungs prevented access to the pulmonary valve and right ventricular outflow tract, two sites commonly in need of attention at surgery. In addition, it was difficult to collect the blood from the pulmonary veins before it entered the left side of the heart. The oxygenated blood could be collected from the left atrium, but that prevented access to the mitral valve and atrial septum.

An oxygenator had to be added to the pump if those limitations of access were to be avoided, so that the venous blood drained from the venæ cavæ could be oxygenated outside the body before being returned to the patient through a cannula inserted into some convenient large artery, such as the femoral, external iliac or subclavian artery, or by "Teflon" graft anastomosis to the aorta. Thus the heart-lung machine consisted of three sections—the venous collection chamber, the oxygenator and the arterial pump.

The first method adopted for collecting the blood from a patient was by cannulating the venæ cavæ and connecting the two cannulæ with a Y piece and wide-bore tube to a venous pump, which both aspirated the blood from the patient and pumped it on to the oxygenator. It was soon found difficult to regulate that pump because the venous return was not constant, particularly in the initial stages of the by-pass. If the setting of the venous pump was too slow, the blood banked up in the venæ cavæ, raising the venous pressure to undesirable heights. If the pump rate was too high, the venous return was inadequate to keep the cavæ walls distended about the cannulæ tips, and the caval walls were sucked into the cannulæ openings. Once that occurred, the pump immediately created a high negative pressure in the line, which tended to keep the walls drawn into the lumen of the cannulaæ. That obstructed the flow of blood from the venæ cavæ.

As a result, pump drainage was abandoned in favour of gravity drainage. The wide-bore tube, which originally connected the Y piece to the venous pump, was now permitted to run into a chamber set below the level of the operating table, so that there was a fall of at least 20 cm. between the venæ cavæ and the level of the blood in the venous collecting chamber. Thus with the cannulæ and the tube filled with blood there was a siphon effect, which could be varied by raising or lowering the table or the venous collecting chamber. The suction pressure created by the siphon was adequate to maintain the venous pressure within normal limits, but was never strong enough to suck the caval walls into the cannulæ and cause obstruction. From the venous chamber, the blood passed either by gravity drainage or pump to the oxygenator.

Three basic types of oxygenator had been designed—the bubbler, the rotating disc and the screen. The uptake of oxygen by hæmoglobin was very rapid. The duration of exposure of the red blood cells to oxygen within the pulmonary capillary was less than one second, but was dependent on their exposure in a thin, probably single cell layer, as they flowed through the capillaries about the air sacs. In designing artificial oxygenators, the aim had been to create thin films of blood within an atmosphere of oxygen. The earliest technique employed was bubbling oxygen through the blood. The numerous small bubbles created an enormous surface area with oxygen in direct contact with the surrounding blood, so that oxygenation was rapid and efficient. Owing to the viscosity of blood, the bubbles tended to persist as a copious foam. The difficulty with that technique lay in defoaming the blood, and in being sure that even minute bubbles were removed before the blood was returned to the patient, otherwise bubble emboli could cause considerable damage, particularly to the brain. With the advent of efficient defoaming agents, the silicone compounds, that had become a practical technique employed in several varieties of bubble oxygenator.

The disc oxygenator created thin films of blood over rotating discs of stainless steel within an atmosphere of oxygen. The filming was achieved, either by having the discs rotate so that the lower sections dipped into a pool of blood, or by running the blood upon the uppermost in a series of discs rotating in an inclined plane, so that the blood fell from plate to plate and was filmed in the process. By that means, a fine blood film was exposed to oxygen without the creation of bubbles and foam.

The last type of oxygenator was the screen. That consisted of sheets of wire gauze set vertically in a frame, so that the blood, run on to the tops of the sheets, passed down the screens and bridged across the spaces in the gauze in a thin film. Once again, with oxygen on either side of the screens, the film of blood was quickly oxygenated without bubbles or foam. The screens were either vertical and stationary or vertical discs rotating about a horizontal axis, or finally the screens were in the shape of cylinders, revolving about a horizontal axis, dipping into a bath of blood.

The final step in extracorporeal oxygenation was the return of the blood under pressure to the patient by means of one of a variety of pumps. The commonest was the roller pump, which gave a pulsatile flow with a fixed stroke volume if the pump was occlusive.

Similarly the finger pump was pulsatile with a fixed stroke volume. Owing to the nature of the occluding action, by roller as against sudden compression with the occluding finger, the roller type tended to be less traumatic, but there was not very much difference between them. Neither of these pumps required valves.

Another pulsatile flow pump consisted of a long metal bar rhythmically compressing a length of plastic or rubber tubing. The stroke volume was varied by controlling the degree of compression of the tubing. Still another variation was the diaphragm pump, either pneumatic or hydraulic. In that pump, either the stroke volume or the rate could be controlled. Those pumps, being non-occlusive, required valves in the input and output ends of the pump chamber. The valves were external and consisted of simple compression levers, which occluded the tubing at appropriate times in the pumping cycle.

While at first it was considered that a pulsatile flow was necessary, several studies had shown that that was not the case, and there were several good reasons why a non-pulsatile flow might be preferable. Since the arterial return was usually through a narrow cannula, compared to the aorta at its origin, the flow of blood through the cannula generated a high pressure in the delivery line, and the blood escaped into the aorta in a jet and created considerable turbulence. Sudden pressure changes and turbulence increased the hæmolysis. A depulsator could be inserted between the pump and cannula to diminish those pressure variations. The depulsator consisted of a length of rubber tubing, which dilated during the systolic phase of the pump action, and in diastole as it returned to its resting state, maintained the flow through the cannula. Air trapped above the level of blood in an arterial reservoir between pump and cannula achieved the same end, the air serving as a cushion and diminishing the pulsatile nature of the flow from the cannula.

A continuous flow pump, such as that employing the Archimedian screw principle, provided minimal pressure variations. In that pump a rotor in the shape of a screw rotated rapidly within a cylinder of rubber or plastic, driving the fluid in the same fashion as a mincing machine, except that the effect on the blood was to move and not mince. That type of pump was one of the least traumatic available. When the blood left the pump, it usually passed through a filter, though the site of the filter could vary, being between oxygenator and pump in some machines. It then returned to the arterial tree of the patient through a cannula or graft.

The Surgical Repair of Intracardiac Defects.

MR. G. WESTLAKE illustrated some principles of open heart surgery using the by-pass machine by discussing the operative management of ventricular septal defect and tetrad of Fallot. He said that an intravenous drip apparatus was set up in the right forearm, and a "Polythene" catheter was inserted into a left forearm vein to be connected to an electromanometer for monitoring venous pressure throughout the operation. A routine endotracheal anæsthetic was then administered and a bilateral submammary thoracotomy made underneath each fourth rib and its cartilage, with transverse section of the sternum. That was the favoured incision, because it gave much better access to all parts of the heart than did the vertical sternal split approach; the latter was a very ugly wound, and more prone to wound infection, especially if a tracheostomy was required.

After the internal mammary vessels had been exposed, one artery was cannulated with a fine "Polythene" cannula,

which was connected to the electromanometer for continuous measuring of arterial pressures during the operation. In smaller patients a radial or femoral artery was used to do that. The pericardium was incised in H-fashion to expose the heart. Mr. Westlake then showed colour slides to illustrate various abnormalities of the heart, and to show how the diagnosis could be made from external inspection of the atria, ventricles and great vessels. The large right side of the heart and pulmonary artery of ventricular septal defect were shown, as well as the small hypertrophied right ventricle with infundibular obstruction and small pulmonary vessels of the tetrad of Fallot. The next step was careful inspection and dissection for a persistent ductus arteriosus, and if a ductus was found it was ligated. Heparin was then administered.

Slides to indicate the various cannulations were then shown. Mr. Westlake stressed that the venous cannulæ passed into the superior and inferior venæ cavæ through the right atrium, and that a cardiotomy sucker cannula was fixed into the left atrium through its appendage and the arterial connexion. Previously a steel cannula had been placed in the femoral artery, but lately a "Teflon" tube was anastomosed to the side of the ascending aorta. Those various cannulæ were connected to the appropriate parts of the heart-lung machine, and the tubings making that connexion were emptied of air and filled with blood prior to the turning on of the by-pass machine.

When all these preparations had been made, the by-pass machine was turned on, and from that moment on, the machine took over the functions of the heart and lungs. It was important at that stage to spend two or three minutes making sure that the by-pass was working satisfactorily before opening the heart.

Mr. Westlake then showed slides of the right ventricle opened up, to illustrate how dry the inside of the heart was during those operations and what an excellent view could be obtained by the surgical team. Intermittent clamping of the aorta was carried out for periods up to five minutes in order to turn off the coronary blood flow. In the intervals when the myocardium was perfused through the coronary vessels, coronary sinus return blood was sucked out with a special cardiotomy sucker, and that blood was returned to the heart-lung machine.

Mr. Westlake went on to say that, should the diagnosis be ventricular septal defect, a decision at that stage of the operation was made regarding the nature of the repair. Several slides showed defects in the membranous septum with a good fibrous margin, which were easily and well repaired by direct suture. However, other defects with only muscle margins, usually much larger ventricular septal defects, were repaired by sewing a patch of "Teflon" into the defect, the patch being fixed in such a way that it lay on the left ventricular aspect of the ventricular septal defect. The reason for that was that the higher left ventricular pressure after the repair acted to force the patch on to the ventricular septal defect when it was fixed in that way, and placed no tension on the mattress sutures holding the defect to the friable heart muscle. Mr. Westlake also showed slides to illustrate how access to the ventricular septal defect could at times be very difficult, owing to the overlying tricuspid valve's septal cusp. Sometimes a papillary muscle had to be divided in order to retract that cusp away from the defect. Such papillary muscle was sutured back to its correct position after the defect had been repaired. Further slides indicated how great care had to be taken during the repair of those defects in order to avoid damage to the aortic valve and the bundle of His, both of which structures were usually in close proximity to the ventricular septal defect.

If the diagnosis was the tetrad of Fallot, there were two main tasks to be performed in the repair; the ventricular septal defect had to be repaired, and the outflow tract of the right ventricle had to be enlarged. The ventricular septal defect of Fallot was repaired in much the same way as an uncomplicated ventricular septal defect. Enlarging the outflow tract from the right ventricle varied from case to case. In a few cases, pulmonary valvotomy was required, with resection of a cylinder of fibrous tissue which was causing severe obstruction to outflow from the right ventricle by narrowing the infundibulum of that chamber. After such fibrous tissue had been resected and pulmonary valvotomy performed, in some cases the infundibular region and main pulmonary artery in cases of tetralogy of Fallot were obviously still far too small to carry a normal cardiac output. In such cases that region of the outflow tract was enlarged by sewing into it a gusset of pericardium or of "Teflon".

Having repaired either the ventricular septal defect or the Fallot situation, the surgical team next prepared to "evacuate" from the heart. One important problem was the removal of all air from the left side of the heart. That was accomplished by turning off the suction of bronchial blood via the left atrial cannula, which manœuvre allowed bronchial blood to fill the atrium and ventricle, expelling air through the ventricular septal defect before the last few sutures in the patch were tied off to close the defect completely. Should the flow of bronchial blood be insufficient for that purpose, the left side of the heart was flooded with saline. Mr. Westlake pointed out that at times air was trapped in the apex of the left ventricle, and that was removed by inserting a large intramuscular needle to allow air to be expelled through the needle during left ventricular systole. Next the ventriculotomy was repaired by direct suture, or in some cases by sewing the gusset into the right ventricle while coronary blood from a coronary sinus filled the right side of the heart, expelling air as it did so.

Once that last stage of heart repair had been completed, the patient was left on heart-lung by-pass for a few minutes, so that the myocardium received an excellent perfusion of oxygenated blood from the aorta before the heart-lung machine was turned off. That gave the heart its best chance to revert quickly to strong sinus rhythm with good ventricular output. When the by-pass machine was turned off the arterial blood pressure was carefully monitored. If the blood pressure remained low, usually that was because the patient had been given an inadequate return of his blood from the machine. That was easily rectified by an aortic perfusion from the machine. However, if it had been decided that blood replacement was complete and the patient still had hypotension, a small injection of adrenaline into the left ventricle usually was sufficient to correct the situation. "Polybrene" was then given intravenously, to neutralize the effect of the heparin, and the various cannulæ, venous and arterial, were removed from the heart and aorta in the last stage of the operation before drain tubes were placed in the chest and the thoracotomy was repaired.

In the post-operative period, the patient was carefully observed for hæmorrhage, heart failure, embolism and heart block. Mr. Westlake showed some slides indicating the treatment of heart block by artificial pacemakers, both the large variety and the small transistorized models, which could be affixed to the patient's pyjamas while he was ambulatory during the convalescent period. Slides were also shown to indicate the end result in cases of tetrad of Fallot, when the patients had been severely cyanosed before the operation and were subsequently pink and healthy looking. It was of particular interest to note that clubbing of the fingers persisted in the early post-operative period, but that the clubbing was bright pink.

Discussion.

DR. M. POWELL said that the three speakers had presented an ideal combination of clinical research, clinical diagnosis and surgery. Their papers showed the importance of the basic factor of teamwork. There had been a fantastic advance in the cardiac surgery performed at the Royal Children's Hospital; the introduction of by-pass techniques was an enormous step forward. One of the most satisfying aspects of that advance had been the approach to the tetrad of Fallot. That had been one of the first conditions for which cardiac surgery had been attempted, but the Blalock procedure had never been a good operation, and its natural history was one of ultimate failure despite temporary success. As the tetrad of Fallot was the commonest cyanotic lesion, an amazing future was opened up.

DR. S. WILLIAMS asked whether much infection occurred.

Mr. Westlake replied that there was little trouble from infection. No antibiotics were administered before operation, although they were given for a few days after operation. Recently he had been spraying the wound with "Neotracin".

DR. M. MCCLELLAND, in answer to a question, said that the anæsthesia for those patients was really quite simple. Before operation "Omnopon" and scopolamine were used, and at operation thiopentone, nitrous oxide and "Tubarine".

DR. R. SOUTHBY asked how soon after the operation the patient was on his feet, and for how long he was in hospital.

Mr. Westlake replied that the patient was usually up on the fourth or fifth day, and went home on the fourteenth day after operation.

Out of the Past.

POLLUTION OF SALTWATER RIVER.[1]

[From the *Australasian Medical Gazette*, June 20, 1902.]

SEVERAL LETTERS have appeared in the *Age* lately as to the pollution of the Saltwater River. It is stated that this river is a scandal to the whole community, and that the law is quite strong enough to prevent its condition, but that the inspectors are either blind or incompetent, and should be replaced by others, who would not fear to do their duty. During the late floods, for hours the river ran black and thick as peasoup and the smell was dreadful: and then the natural silt came, and for a few weeks after the water was clear and clean. Now once more viscera and filth are beginning to float about, and each day takes away some of the good done by the flood. The river is far superior to the Yarra in many respects, and should be a source of delight to fishermen and boating parties. It is also navigable for crafts of considerable size some miles above the junction with the Yarra: but all this is destroyed in the interests of a few slaughter-yards, and the whole district contaminated with horrible smells and a deposit of disgusting filth on its banks. Sydney has had to pay dearly for like neglect, and it is quite time that the Government insisted that the health of thousands should not be endangered by the neglect of inspectors and interested parties.

Correspondence.

AN AUSTRALIAN MEDICAL ASSOCIATION.

SIR: In determining the ultimate constitution of the proposed Australian Medical Association, I think we have got to be quite clear in our minds as to whether the Association will be primarily a national body of our profession in its conception and spirit, of which the State Councils will be but branches, or whether the Association, as embodied in the proposed Assembly and Federal Council, will be in actuality an occasional liaison between the Councils elected in the various States. Our attitude towards this fundamental question will need to be reflected in the method by which the Assembly and Council are elected.

I would enter the plea that our vision be essentially a national one, and that the composition of the Assembly be determined by a method of election which will be as directly as possible responsible towards, and representative of, the rank and file of practising members throughout the Commonwealth. I would draw attention to the fact that in these days, when medical practice is assuming greater and greater political importance, State boundaries have no significance. It is most important that, in the supreme councils of our profession, there will be a reflection of the fact that we are indeed one profession and speak with one mind.

Yours, etc.,

KENNETH N. GRIGG.

Rosanna Medical Centre,
Melbourne, N.22,
Victoria.
April 29, 1961.

THE MANAGEMENT OF TETANUS.

SIR: In THE MEDICAL JOURNAL OF AUSTRALIA, April 29, 1961, there are several articles and a "Current Comment" which are confusing and misleading. Anyone who has treated severe tetanus must be impressed by the extreme variations in severity and patient response to the disease. Any deductions drawn from a single case are unimpressive; but to encourage others to follow a line of treatment in itself dangerous, as suggested by Maddocks and Dawborn, is open to severe criticism. This is more so when it is supported by an authoritative review from Wood and Mackay.

As stated in your editorial comment, the clinician aims to be in complete control throughout the patient's illness. We do not regard major spasms for six days and minor spasms for twelve days as adequate control. Such management in middle-aged and elderly people would be invariably fatal, and the authors are fortunate that their experience has been confined to two fit young patients.

Wood and Mackay state that emergency tracheostomy could be required before transport is undertaken. Bearing in mind that fact that the site and size of the tracheotomy will have a great bearing on the future management of the patient, we feel that emergency tracheotomy is never necessary. Transport can be easily arranged with an endotracheal tube *in situ*, and there is no place for a rushed, unplanned, inadequate tracheotomy by inexperienced personnel.

In general we agree with Dr. Clifton's approach to the problem; but we prefer earlier and complete paralysis with "Tubarine" in all but the very mild cases. Experience with heavy sedation alone, large doses of chlorpromazine alone, a combination of the two, partial and finally complete paralysis with "Tubarine", has led us to feel that the latter approach is best. It also avoids the confusing effects of polypharmacy. It appears unreasonable to suggest control of spasms by a combination of meprobamate, chlorpromazine, promethazine and barbiturates as postulated by Perlstein, when one drug, *d*-tubocurarine, virtually devoid of side effects, will be completely effective regardless of external stimulation.

We would add to Dr. Clifton's suggestions the following points: (*a*) Humidification. This is important in order to avoid large plugs of hard, sticky sputum which may cause disaster. This is provided adequately by a Radcliffe humidifier, and most aerosols and atomizers are useless. (*b*) Respirators. We have found the Radcliffe respirator simple, effective and mechanically sound. (*c*) Electrolyte requirements. These patients lose large amounts of potassium in the urine secondary to cellular disturbances. They are often in negative balance when first seen, and may require six to eight grammes of potassium chloride by intravenous injection daily. This is estimated from the urinary loss, and illustrates the importance of daily urinary electrolytes. (*d*) Curarization should not be the last resort. It should be the first in severe cases. (*e*) The patients can only be managed by a specialized unit at a large hospital.

Finally, at a time when controversy ranges as to the correct treatment of this disease, it is unfortunate that Dr. Clifton's excellent review does not contain any figures from the Royal Prince Alfred Hospital.

Yours, etc.,

BRIAN DWYER,
Director of Anæsthesia.

JOHN B. HICKIE,
Senior Lecturer in Medicine.

St. Vincent's Hospital,
Sydney.
May 2, 1961.

PRESCRIPTION FORMS.

SIR: I notice that the B.M.A. Federal Council has persuaded the Government to cease printing prescription pads.

I was unaware of the existence of these pads till a few months ago, and I was delighted to find that there was an unlimited supply of them and that they were sent free of charge. They are an ideal pad, superior to the articles that the printers have produced for me over the years and costing about 8s. 6d. each.

Why has the Federal Council passively accepted the numerous regulations and restrictions which the Government has laid down, and then violently objected to the only sensible and helpful thing the Government has ever done? Surely when a person is told by someone that he must write something in duplicate, the reaction of any intelligent individual would be: "All right, well *you* supply the forms!"

To understand is to forgive, and if any of your readers can explain the peculiar behaviour of the B.M.A., I might forgive them.

Yours, etc.,

C. GAME.

258 Dorset Road,
Boronia,
Victoria.
April 23, 1961.

[1] From the original in the Mitchell Library, Sydney.

Notes and News.

Nuffield Foundation Dominion Travelling Fellowships.

The Nuffield Foundation will continue in 1962 its scheme of offering a number of Travelling Fellowships to Australian graduates. Seven awards will be available in medicine, the natural sciences and the humanities and social sciences.

The purpose of the fellowships is to enable Australian graduates of outstanding ability to gain experience and training in the United Kingdom in their chosen fields, and to make contact there with scholars working in those fields, with a view to the Fellows equipping themselves to take up posts in teaching and/or research in Australia.

The fellowships are intended for men or women of first-rate intellectual and personal qualities, who have already shown unusual capacity to advance knowledge and teaching in one of the fields concerned. The Foundation wishes the awards to be open on as wide a basis as possible, and it is intended that the broad divisions listed above should cover such fields as dentistry, veterinary science, agriculture, engineering, architecture, etc. Candidates must be Australian citizens (persons either born in Australia or who have become Australian citizens), normally between the ages of 25 and 35 years, and must be university graduates holding, preferably, a master's or doctor's degree, and having subsequently had a year or more of teaching or research experience on the staff of a university or comparable institution.

A fellowship will normally be tenable for one year, but in exceptional cases may be extended for a further period of a few months. A Fellow will be expected to resume residence in Australia on completion of the fellowship.

The value of the award will be at the rate of from up to £1290 (single) to up to £1490 (married and accompanied by wife). In addition, the Foundation will pay the return travelling expenses of the Fellow, and of his wife if she spends a minimum of six months with him in the United Kingdom. The allowance for sea passages will be the equivalent of the best tourist rate available; the Foundation can only reimburse the travel agency concerned by payment in sterling direct to the London agents, and cannot reimburse the Fellow direct. No allowance can be made for children's travelling expenses, nor can any part of the travel allowance be saved and used for this purpose.

Except with the express permission of the trustees of the Foundation, a Fellow may not hold any other award concurrently with the fellowship. A Fellow will be required to carry out, at centres approved by the trustees of the Foundation, a programme of research work and training, similarly approved. Other work, paid or unpaid, may not be undertaken without the permission of the trustees. During the tenure of the fellowship a Fellow will not normally be permitted to prepare specifically for, or to take, examinations for higher degrees or diplomas awarded by bodies in the United Kingdom.

A Fellow will be required to submit to the trustees, at the end of the fellowship, a report on his work during the period of fellowship.

Should the trustees at any time find that a Fellow neglects or has neglected the obligations of the appointment, they shall have power immediately to terminate the fellowship.

The fellowships will be awarded by the trustees of the Foundation on the recommendation of its Advisory Committee in Australia.

Applications for fellowships to begin in 1962 should be submitted not later than Friday, August 11, 1961, to the Secretary, The Nuffield Foundation Australian Advisory Committee, Engineering Chemistry Laboratory, University of Melbourne, Parkville, N.2, Victoria, from whom copies of the application form may be obtained. Applications must be accompanied by a programme of intended work in the United Kingdom in as specific terms as possible.

Course in Plastic Surgery in England.

The British Council announces that a course in plastic surgery will be held on October 1 to 14, 1961, at East Grinstead and Oxford. The course is designed to give a comprehensive picture of the field of plastic surgery, maxillo-facial surgery and allied specialist subjects. The first part of the course will last from October 1 to 11, and will be spent at the Queen Victoria Hospital, East Grinstead. The programme will consist of one or more lectures per day, describing the role of plastic surgery in congenital deformity, in traumatic injuries and in deformities resulting from burns and disease. The lectures will be completed by a full programme of observations in the operating theatre. The second part of the course will begin on October 12, and will consist of a two-day visit to the Department of Plastic Surgery at the Churchill Hospital, Oxford. The course is intended for surgeons from overseas specializing in plastic surgery. They should have considerable background of general surgery and intend to broaden their experience in the reconstructive field. As a guide to the extent to which this would be expected, it is pointed out that in Great Britain surgeons who specialize in plastic surgery are required to have four years of first-class surgical experience after graduation. The course will be limited to 20 members. Applications and requests for further information should be addressed to The British Council, 18 Greenoaks Avenue, Edgecliff, Sydney, N.S.W.

Seventh Therapeutics Congress.

The seventh Congress of the International Union for Therapeutics will be held at Geneva from October 6 to 8, 1961, under the presidency of Professor G. Bickel, Director of the Medical Clinic of the University of Geneva. The Congress will deal exclusively with the following subjects: trypsin and chymotrypsin; fibrinolytic enzymes; monoamino oxidase inhibitors; carbonic anhydrase inhibitors; hormone inhibitors. Further information may be obtained from the General Secretary of the Organizing Committee at the following address: Dr. P. Rentchnick, Case postale 229, Geneva 4, Switzerland.

Post-Graduate Committee in Medicine in the University of Sydney: Training Fellowship in Psychiatry.

The Senate of the University of Sydney has awarded a Post-Graduate Training Fellowship in Psychiatry to Dr. Anna Gregory, of East Lindfield, New South Wales.

N. E. Goldsworthy and H. R. Sullivan Memorial Prize.

To honour the names of two distinguished graduates of the University of Sydney, the Dental Alumni Society of the University of Sydney has inaugurated a fund to endow a prize, to be known as the N. E. Goldsworthy and H. R. Sullivan Memorial Prize. Dr. Goldsworthy was widely known for his academic achievements in bacteriology and as the Director of the Institute of Dental Research since its inception. Dr. Sullivan distinguished himself in dental practice, in military service and as Assistant Director of the Institute of Dental Research. The prize is to be awarded annually to an undergraduate in the Faculty of Dentistry, University of Sydney, for an essay (if of sufficient merit) on some aspect of oral biology. Such a prize is considered appropriate to the memory of Neil Goldsworthy and Harold Sullivan, whose interests and achievements lay in this field. Donations to this fund will be gratefully received from all interested persons, and should be sent to The Honorary Secretary, The Dental Alumni Society of the University of Sydney, c.o. United Dental Hospital, 2 Chalmers Street, Sydney.

American Heart Association: Leaflet on Innocent Heart Murmurs in Children.

A new leaflet to help physicians allay parents' unwarranted fears when children are diagnosed as having innocent or functional heart murmurs has been issued by the American Heart Association and its affiliates. Written in simple lay terms, the four-page leaflet emphasizes the harmlessness of innocent murmurs in children and explains why the family physician and/or heart specialist may wish to reexamine such children periodically. It notes also that organic murmurs indicate the presence of a disease or heart defect, and points out that "any child with an organic murmur needs the supervision and care of a physician". The leaflet is entitled "Innocent Heart Murmurs in Children". Copies for distribution to parents may be requested by physicians from local heart associations, or from the American Heart Association, 44 East 23rd Street, New York 10, N.Y.

Poliomyelitis Vaccine.

According to a statement issued by the Minister for Health, Dr. D. A. Cameron, the Commonwealth Department of Health has imported a supply of poliomyelitis vaccine from Canada, in case current difficulties with testing of the vaccine at the Commonwealth Serum Laboratories persist. Dr. Cameron said that it was desirable that the vaccine should be tested on arrival. This was not because the

sterility of the vaccine would be in any way in doubt, but as a matter of responsibility. The Government held that it should not distribute an imported vaccine unless it could itself accept full responsibility for the safety and potency of the vaccine. It was probable that the Commonwealth Serum Laboratories would soon overcome its testing problems, and adequate supplies would become available from the laboratories shortly. However, it was considered advisable to have an emergency imported stock on hand, in case the present difficulties were not overcome as soon as was hoped. Accordingly an emergency supply had been procured. The supply could be increased at a later stage, in the unlikely event of its proving necessary to do so.

Rockefeller Foundation Grants.

The following are among the Rockefeller Foundation Grants for the first quarter of 1961.

The Australian National University, Canberra, has received a grant of $5000 for research equipment and supplies for use in the Department of Physiology under the direction of Professor Sir John Eccles.

Dr. G. J. V. Nossal, Research Fellow of the Walter and Eliza Hall Institute of Medical Research, Melbourne, and currently Assistant Professor of Genetics, School of Medicine, Stanford University, Palo Alto, California, has received a grant of $4590 to visit centres of research in immunology and genetics in the United States, Europe and Israel while en route from the United States to Australia.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Course in Liver Diseases.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that a course in liver diseases will be conducted in the Department of Medicine on Tuesdays and Thursdays, 4.30 to 6 p.m. from July 11 to August 17, 1961, under the supervision of Professor C. R. B. Blackburn. The course will cover physiological, biochemical and clinical aspects of liver disease and is designed for physicians and for those studying for higher degrees or diplomas. Subjects to be covered will include biliary obstruction, protein metabolism and hepatic coma, acute liver injury, chronic liver disease, portal hypertension and bleeding œsophageal varices, ascites, cirrhosis of the liver, metabolic disorders and liver function tests.

The fee for attendance is £6 6s., or £3 3s. for full-time hospital registrars. A detailed programme will be available shortly. Those wishing to enrol are asked to communicate with the Course Secretary, The Post-Graduate Committee in Medicine, Herford House, 188 Oxford Street, Paddington, New South Wales, at an early date. Telephone: FA 0671. Telegraphic address: "Postgrad Sydney".

Notice.

THE ENDOCRINE SOCIETY OF AUSTRALIA.

Annual Meeting, 1961.

THE annual meeting of the Endocrine Society of Australia will be held at the Department of Chemistry, University of Queensland, on Thursday and Friday, May 25 and 26, 1961. The programme is as follows.

Thursday, May 25: 2 p.m., Report of council proceedings; presidential address, "Anti-Fertility Agents", C. W. Emmens; 3 p.m., "The Early Metabolic Effects of Desiccated Thyroid, Thyroxine and Triiodothyronine in Man: Comparison with Early Effect of Thyrotrophic Hormone", B. S. Hetzel, M. L. Wellby and B. F. Good (read by B. S. Hetzel); 4 p.m., "Preparation of Human Growth Hormone", A. L. Wallace and K. A. Ferguson; 4.15 p.m., "The Prolactin Activity of Human Growth Hormone", K. A. Ferguson and A. L. Wallace; 4.30 p.m., discussion of the foregoing two papers; 4.45 p.m., "The Use of Enzymes in the Diagnosis of Pancreatitis", W. Roman and R. Pain (read by W. Roman).

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED APRIL 8, 1961.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	1(1)	..	..	1(1)	..	..	..	3
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	4	..	4
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	..	..	..	..	..
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	4	41(35)	5(5)	..	..	..	8	..	58
Diphtheria	..	..	..	..	1	..	..	..	1
Dysentery (Bacillary)	..	5(1)	..	..	5(4)	..	5	..	15
Encephalitis	..	..	..	..	..	..	..	..	..
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	76(33)	136(48)	9	18(10)	3(2)	10(1)	..	3	255
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	5	..	..	..	..	..	5
Malaria	..	..	1(1)	..	..	..	..	1	2
Meningococcal Infection	1	..	..	..	..	..	..	..	1
Ophthalmia	..	..	..	..	1	..	..	..	1
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	4(2)	..	1(1)	..	..	..	..	5
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella	..	5(1)	..	..	3(2)	..	..	..	8
Salmonella Infection	..	..	..	..	3	..	..	1	4
Scarlet Fever	1	7(6)	3(1)	1	..	2	..	..	14
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1	..	..	..	..	..	1
Trachoma	..	..	..	..	1	..	4	..	5
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	5(3)	14(12)	4(1)	4(4)	6(3)	2(1)	..	..	35
Typhoid Fever	..	..	..	..	..	..	1	..	1
Typhus (Flea-, Mite- and Tick-borne)	..	..	1(1)	..	..	..	..	..	1
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Friday, May 26: 9.30 a.m., "The Effect of Œstrogen on the Uterine Uptake of Phosphorus-32", G. Stone; 10 a.m., "Some Aspects of the Metabolism of Injected Progesterone in the Liver", M. G. Brush (by invitation); 10.30 a.m., "Recent Studies on the Mode of Action of Œstrogens in the Vaginal Epithelium of the Mouse", L. Martin; 11.30 a.m., "A Method for Studying the Secretion of the Intact Adrenal Gland in Conscious Sheep", I. R. McDonald; 12 noon, "2-Hydroxyœstrone and Related Œstrogen Metabolites", R. I. Cox; 12.30 p.m., "Beta-Glucuronidase from Female Rat Preputial Gland: Its Use in Hydrolysis of Steroid Conjugates", B. Hudson, A. Dulmanis and J. Sheath (read by B. Hudson); 2.15 p.m., "Some Queries Regarding the Adrenocortical Response to Corticotrophin", A. W. Steinbeck; 2.45 p.m., "Evidence of a Hormonal Influence on the Steroid Output of an Adrenal Carcinoma", F. I. R. Martin; 3.45 p.m., "Intrathoracic Goitre: Review of 134 Cases", T. S. Reeve; 4.15 p.m., "The Use of Corticosteroids in Thyroid Ophthalmopathy", I. B. Hales and I. D. Thomas (read by I. B. Hales).

Professor Douglas Hubble, Professor of Pædiatrics, University of Birmingham, will be attending the meeting and will take part in the discussions.

Royal Australasian College of Surgeons.

VICTORIAN STATE COMMITTEE: POST-GRADUATE COURSE IN SURGERY.

THE Victorian State Committee of the Royal Australasian College of Surgeons is arranging a course of instruction in post-graduate surgery to be held in Melbourne from July 31 to October 6, 1961. The course will be full time. During the mornings entrants will, with some restrictions, be able to attend and observe the work in the various clinical schools. Tuition will begin each week-day at 2 p.m., and at 4 p.m. on each day there will be a session on clinical surgery. The course has been so arranged as to enable anyone who wishes to do so to take off 12 weeks prior to the final examination for the Fellowship of the Royal Australasian College of Surgeons in October, to prepare for this examination. In addition, the clinical instruction is being conducted in the late afternoons, in order that senior resident medical officers may be able to attend this part of the course.

The fees for the course are: (*a*) full time, 20 guineas; (*b*) clinical only, 10 guineas. Entries for the course close on July 14, 1961. Candidates when entering must forward a remittance for the fee—20 guineas or 10 guineas as the case may be—plus exchange, in the case of candidates resident in Australia, for cheques drawn on banks outside Melbourne. Candidates resident in New Zealand or elsewhere should remit by bank draft drawn on Melbourne in favour of the Royal Australasian College of Surgeons, and payable in Asutralian currency. Applications should be directed to the Honorary Secretary, Victorian State Committee, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Davis, Geoffrey Lancelot Rutter, M.B., B.S., 1958 (Univ. Sydney), Kanematsu Institute, Sydney Hospital, Sydney.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Cellermajer, John Marian, M.B., B.S., 1960 (Univ. Sydney); Chang, Peter Nan-Sang, M.B., B.S., 1960 (Univ. Sydney); Davis, Colin George, M.B., B.S., 1960 (Univ. Sydney); Henson, Ross William, M.B., B.S., 1955 (Univ. Sydney); Jones, Brian Montford, M.B., B.S., 1961 (Univ. Sydney); Long, Geoffrey Joseph, M.B., B.S., 1959 (Univ. Sydney); O'Rourke, Michael Francis, M.B., B.S., 1960 (Univ. Sydney); Salemann, Constantine, M.D., 1941 (Univ. Tartu), registered under Section 17 (2B) of the Act; Stening, George Frank Hugh, M.B., B.S., 1961 (Univ. Sydney); Vines, Arthur Peter, M.B., B.S., 1956 (Univ. Sydney); Tziniolis, John, M.D., 1951 (Univ. Athens), licensed under Section 21 (c4) of the Act; Farnsworth, Robert Housley, M.B., B.S., 1960 (Univ. Sydney); Lecky, Jocelyn Olive Helen, M.B., B.S., 1960 (Univ. Sydney).

Deaths.

THE following death has been announced:

GROVER.—Harley Grover, on April 22, 1961, at East Brighton, Victoria.

Diary for the Month.

MAY 15.—Victorian Branch, B.M.A.: Finance Sub-Committee.
MAY 16.—New South Wales Branch, B.M.A.: Medical Politics Committee.
MAY 17.—Western Australian Branch, B.M.A.: General Meeting.
MAY 18.—New South Wales Branch, B.M.A.: Clinical Meeting.
MAY 18.—Victorian Branch, B.M.A.: Executive Meeting of Branch Council.
MAY 19.—New South Wales Branch, B.M.A.: Ethics Committee.
MAY 19.—Queensland Branch, B.M.A.: Council Meeting.
MAY 20.—Victorian Branch, B.M.A.: Country Branch Meeting.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): Medical Officers to Sydney City Council. All contract practice appointments in New South Wales. Members are requested to consult the Medical Secretary before undertaking practice in dwellings owned by the Housing Commission.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full data in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: MW 2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in Australia can become subscribers to the Journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £6 *per annum* within Australia and the British Commonwealth of Nations, and £7 10s. *per annum* within America and foreign countries, payable in advance.